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# Brain

67

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**Kufs' disease. A critical reappraisal.** S. F. Berkovic, S. Carpenter, F. Andermann, E. Andermann and L. S. Wolfe 27

**Human saccadic eye movements in the absence of the geniculocalcarine projection.** J. L. Barbur, P. M. Forsyth and J. M. Findlay 63

**The characterization of experimental gliosis by quantitative nuclear magnetic resonance imaging.** D. Barnes, W. I. McDonald, D. N. Landon and G. Johnson 83

**The localization of the lesion in patients with acute ophthalmoplegia, ataxia and areflexia (Miller Fisher syndrome). A serial multimodal neurophysiological study.** G. A. Jamal and J. P. Ballantyne 95

**Ocular motor deficits in Parkinson's disease. III. Coordination of eye and head movements.** O. B. White, J. A. Saint-Cyr, R. D. Tomlinson and J. A. Sharpe 115

**Spatial frequency-dependent abnormalities of the pattern electroretinogram and visual evoked potentials in a parkinsonian monkey model.** M. F Ghilardi, I. Bodis-Wollner, M. C. Onofrj, M. S. Marx and A. A. Glover 131

**Slowly progressive aphasia in three patients. The problem of accompanying neuropsychological deficit.** K. Poeck and C. Luzzatti 151

**Intellectual function following penetrating head injury in Vietnam veterans.** J. Grafman, B. S. Jonas, A. Martin, A. M. Salazar, H. Weingartner, C. Ludlow, M. A. Smutok and S. C. Vance 169

**Remote memory function in Alzheimer's disease and Parkinson's disease.** H. J. Sagar, N. J. Cohen, E. V. Sullivan, S. Corkin and J. H. Growdon 185

**Postural effects on F wave parameters in lumbosacral root compression and canal stenosis.** L. M. Tang, M. S. Schwartz and M. Swash 207

**Book reviews** 215

**Announcements** 220

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67

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# THE EPIDEMIOLOGY OF MULTIPLE SCLEROSIS IN THREE AUSTRALIAN CITIES: PERTH, NEWCASTLE AND HOBART

*by* S.R. HAMMOND[1], J.G. McLEOD[1], K.S. MILLINGEN[2], E.G. STEWART-WYNNE[3], D. ENGLISH[5], J.T. HOLLAND[4] *and* M.G. McCALL[6]

*(From the Departments of Medicine, [1]University of Sydney and [2]University of Tasmania, the Departments of Neurology, [3]Royal Perth Hospital and [4]Royal Newcastle Hospital, and the [5]NH and MRC Research Unit in Epidemiology and Preventive Medicine, Perth and the [6]Department of Extended Care, Sir Charles Gairdner Hospital, Perth, Australia)*

## SUMMARY

An epidemiological survey of multiple sclerosis (MS) in three Australian cities, Perth, Newcastle and Hobart, was undertaken with its prevalence day being the national census day on June 30, 1981, exactly twenty years after a previous survey of the same cities. The relationship between increasing prevalence and increasing south latitude found in the 1961 survey was confirmed in this present study. Prevalence rates had increased significantly over the twenty years between the studies. Over the same time period incidence rates had also increased in Newcastle and Hobart but had remained essentially stable in Perth although these changes were not significant. The rise in prevalence was due to a combination of factors of differing importance in each city. These factors included better case ascertainment, increased recognition of the less severely disabled patient, increased survival time and differential immigration of a population at a higher risk of developing MS than the indigenous population. Finally, analysis of MS prevalence rates amongst migrant populations in Perth and Hobart suggested that either the risk of acquisition of MS may extend over a wider age range than is generally accepted or that environmental factors prevalent in the former city have modified disease expression there.

## INTRODUCTION

In 1961 an epidemiological study of multiple sclerosis (MS) was conducted in three Australian cities: Perth, the capital of Western Australia, Newcastle, the second largest city in New South Wales, and Hobart, the capital of Tasmania (McCall *et al.*, 1968). This survey, together with that of Sutherland *et al.* (1966) in Queensland, established that a gradient of frequency of MS existed within Australia, the disease becoming increasingly frequent with increasing distance from the equator. However, since that time no further similar studies have been conducted within

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Australia. The aim of this study therefore was to resurvey these three cities to assess whether any of them had experienced any change in the prevalence and incidence of MS.

Population figures were available for each city from the census taken on June 30, 1981 and thus this date, exactly twenty years later than the previous survey, was chosen as the prevalence day for the present survey.

## GEOGRAPHICAL NOTE (fig. 1)

Metropolitan Perth is situated on the Swan river at latitude 31°57'S, longitude 115°52'E and its statistical division covers an area of 5306 $km^2$. In June 1961 the population was 420,133 but by June 1981 this had grown to 898,918 Immigrants accounted for 23.9% of the population in 1961 and 31.6% in 1981.

The city of Newcastle is situated on the Hunter river at latitude 32°52'S, longitude 151°49'E, covering an area of 205 $km^2$. In June 1961 the population was 142,574 but by June 1981 this had fallen to 135,207 with about half of this minor exodus taking place in the previous 5 years (the population in June 1976 was 138,719). Immigrants accounted for 11.7% of the population in 1961 and 14.2% in 1981.

The statistical division of Hobart is situated at latitude 42°50'S, longitude 147°21'E, straddling the estuary of the Derwent river and covering an area of 940 $km^2$. In June 1961 the population was 115,932 but by June 1981 this had grown to 168,363. Immigrants accounted for 12.1% of the population in 1961 and 12.6% in 1981.

Details relating to the industries and climate of each area have been published previously (McCall *et al.*, 1968). Medical facilities in each of these centres are of similar quality, based on a number of major teaching hospitals where record keeping is of good standard. In each centre the number of practising doctors per head of population is of the order of 1 in 500. Diagnostic indices have been in existence in the principal hospitals in Perth and Hobart since 1955 and in Newcastle since 1951.

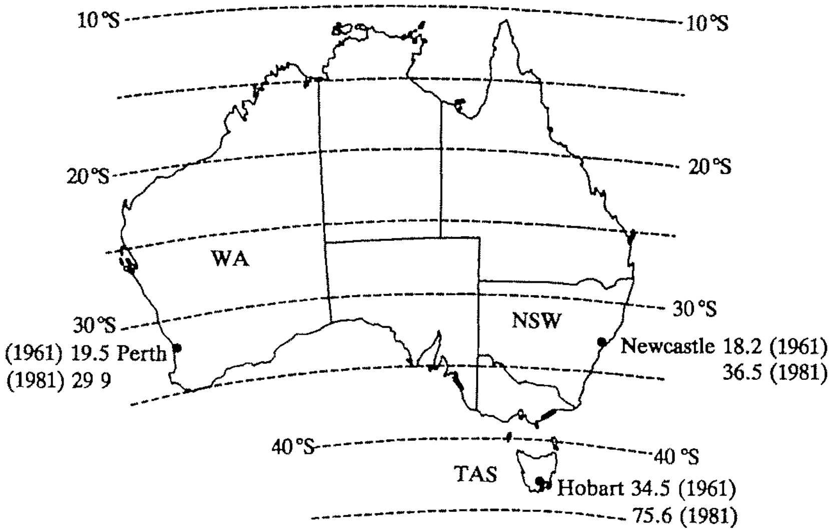

FIG. 1 Map of Australia showing locations of Perth in Western Australia (WA), Newcastle in New South Wales (NSW) and Hobart in Tasmania (TAS) with their respective age-standardized (1981 Australian population) prevalence rates of MS in 1961 and 1981.

## METHODS

The methods employed in collecting medical data were similar in each centre and closely followed those employed in the 1961 survey Standardization of these procedures was ensured by regular meetings of survey coordinators from each area. The major sources for case ascertainment were as follows. (1) Diagnostic indices of the major hospitals in each area. (2) Practising doctors—a circular letter was sent to all neurologists, internal medicine specialists, neurosurgeons and general practitioners in each of the areas, requesting the name, most recent address, approximate date of diagnosis and hospital where notes might be found, of any patient known to them, either currently or in the past, in whom the likely diagnosis was MS. Follow-up procedures included a second mailing of this letter if no reply was received to the first, and personal telephone calls in some instances. (3) MS Societies—in each area the cooperation of the local MS Society was enlisted. For Newcastle this also involved a complete search of the records of the New South Wales State MS Society based in Sydney. (4) Department of Veteran Affairs State Diagnostic Indices in each area. (5) Chronic care hospitals in and adjacent to the areas of survey. (6) Commonwealth statistician—in each area a request was made to notify the survey of any deaths from MS subsequent to prevalence day (June 30, 1981).

Because of Newcastle's close proximity to Sydney, similar procedures were followed in Sydney, searching for cases having addresses in the Newcastle area.

In addition to these sources there were others which were peculiar to the particular State in which the survey area lay. For instance, in New South Wales the State Hospital Morbidity Survey was used, whereas in Tasmania the survey was able to call upon a State Chronic Care Hospital Register and to request from the Commonwealth Department of Health notification of cases of suspected MS applying for financial assistance, an invalid pension or for long term/increased quantities of steroids for management of their disease.

Details of doctors' records and hospital admission notes were transferred to a standard protocol form which was specially designed to facilitate entry of its information into a computerized data base. Permission for the surveyors (all of whom were neurologists) to contact all notified patients was obtained in each area and subsequently these patients were all interviewed personally and examined. All patients in whom the diagnosis of MS was considered to be correct were then classified according to the diagnostic criteria of Rose *et al.* (1976) into Clinically Definite, Probable or Possible groups. It should be stressed that no laboratory results (e.g., CSF analysis, evoked potential studies or CT brain scans) were considered in the allocation of individual patients to particular diagnostic categories. The disability status of the patients on prevalence day was assessed according to the Kurtzke disability status scales (DSS) (Kurtzke, 1970).

A 10% sample of the protocol forms from each survey area was selected on an alphabetical basis and submitted to an independent neurologist arbiter for assessment of the correctness of the diagnosis and of the diagnostic classification into which each patient had been placed. For Newcastle the sample was drawn from the survey of the whole Newcastle statistical district (1981 census population 389,235) in order that the number of reviewed cases be of a similar order to the other two survey areas.

### *Definitions*

Crude prevalence was defined as the ratio of persons with an acceptable diagnosis of MS living in the defined area on June 30, 1981 (national census day) to the total number of persons in the population of the same area on the same day, and was expressed per 100,000 of population.

Crude incidence was calculated from the number of cases ascertained in which the onset of symptoms occurred during the decade from June 30, 1971 to June 30, 1981 within the defined area, and was expressed per 100,000 person years using the census population at June 30, 1976 as the denominator.

Crude mortality was estimated from the number of deaths ascertained by two methods of data collection. The first or indirect method of data collection involved ascertaining from the Australian

Bureau of Statistics (ABS) the number of deaths from MS notified to them in the decade 1971 to 1980; this consisted of only those patients in whom MS was stated as the underlying cause of death. The second or direct method involved collecting data for each MS patient with reference to 2 separate 'prevalence days' five years apart (June 30, 1976 and 1981, the last 2 national census days), and recording the number of patient deaths in this time period; this method included deaths from all causes. Mortality rates derived from both sources were expressed per 100,000 person years, the denominators for data collected by the indirect and direct methods being the census population at June 30, 1976, and the average of the census populations at June 30, 1976 and 1981, respectively.

Female: male ratios were calculated by persons, as is customary, not rates.

### *Statistics*

Crude morbidity and mortality rates from the 1961 (McCall *et al.*, 1968) and present surveys were age-corrected or age-standardized to the distribution of the total Australian population on June 30, 1981 wherever possible, to facilitate direct comparisons. However, age-specific rates were not available for the incidence data of the 1961 survey (McCall *et al*, 1968). Therefore, comparisons of incidence between the two surveys were based upon rates age-standardized to the distribution of the 1954 census populations in each city, this being the census population closest to the midpoint of the incidence decade 1950–59 used in the 1961 survey. Differences between age-standardized rates were analysed by the method of Knowler *et al.* (1978).

Comparisons of crude rates which could not be age-standardized to the same population for lack of age-specific rates, used a test for the significance of the difference between two Poisson variables, because estimated rates of morbidity or mortality can be considered as being the mean of a Poisson distribution in a disease with low frequency such as MS (Schoenberg, 1983). Confidence intervals (CI) for individual rates were calculated from tables based on the Poisson distribution (Schoenberg, 1983). The relationship between latitude and prevalence and mortality rates was analysed using Armitage's test for linear trends in proportions and frequencies (Armitage, 1955). The $\chi^2$ test was used to test the statistical significance of differences between the distribution of various clinical parameters in the 3 survey areas. Differences were considered statistically significant when $P<0.05$.

## RESULTS

### *Comparability of case ascertainment and diagnostic classification*

In Table 1 a comparison is made between the proportion of cases ascertained in various ways in the three areas for the 1981 prevalence day. Many of the patients had multiple sources of referral. The average number of sources reporting each case was highest for Newcastle (3.2), closely followed by Hobart (2.9) while Perth (2.3) had the lowest figure. Substantial differences in the sources of referred cases were apparent between the survey areas.

Complete agreement between the area surveyors and the independent neurologist arbiter concerning the 10% case sample was present in 70, 94 and 80% of cases from Perth, Newcastle and Hobart, respectively, whereas there was a difference of opinion concerning diagnostic categorization in the remainder of the patients in each city. No patients were deemed to require exclusion on the basis of an incorrect diagnosis. The level of agreement was not significantly different in the three cities ($\chi^2$ 4.5, $0.1<P<0.5$).

In Table 2 the proportions of patients allocated to each diagnostic category are compared in each city. It should be noted that in 1961 the diagnostic criteria of

TABLE 1 MEANS OF ASCERTAINMENT OF 1981 PATIENTS IN EACH CENTRE*

| *Source of case* | *Perth* | *Newcastle* | *Hobart* | *Significance* |
|---|---|---|---|---|
| Hospital diagnostic index | 109 (41) | 48 (94) | 77 (62) | $P<0.001$ |
| Neurologist | 139 (53) | 43 (84) | 97 (78) | $P<0.001$ |
| Other physician | 20 (8) | 11 (22) | 33 (26) | $P<0.001$ |
| General practitioner | 141 (53) | 19 (37) | 75 (60) | $P<0.05$ |
| MS Society | 126 (48) | 30 (59) | 40 (32) | $P<0.01$ |
| Other | 68 (26) | 11 (22) | 35 (28) | |
| Total no. of patients | 264 | 51 | 125 | |
| Average no. of sources per reported case | 2.3<br>[3.0] | 3.2<br>[2.0] | 2.9<br>[2.5] | |

* The figures in ordinary parentheses are percentages. The figures in square parentheses are the average number of sources per reported case in 1961.

TABLE 2 DIVISION OF PATIENTS BY DIAGNOSTIC CATEGORY IN 1961 AND 1981 FOR EACH CITY AND FOR THE 3 CITIES COMBINED*

*Cases in each diagnostic category*

| | *Definite* | | *Probable* | | *Possible* | | *Total* | |
|---|---|---|---|---|---|---|---|---|
| *City* | *1961* | *1981* | *1961* | *1981* | *1961* | *1981* | *1961* | *1981* |
| Perth | 70 (66) | 184 (70) | 23 (22) | 34 (13) | 13 (12) | 46 (17) | 106 | 264 |
| Newcastle | 24 (73) | 35 (69) | 4 (12) | 11 (21) | 5 (15) | 5 (10) | 33 | 51 |
| Hobart | 36 (65) | 91 (73) | 14 (25) | 24 (19) | 5 (9) | 10 (8) | 55 | 125 |
| 3 cities | 130 (67) | 310 (70) | 41 (21) | 69 (16) | 23 (12) | 61 (14) | 194 | 440 |

* The figures in parentheses are percentages

Allison and Millar (1954) were used and for this comparison their 'probable', 'early probable' and 'possible' categories have been considered to be equivalent to the 'clinically definite', 'probable' and 'possible' categories of Rose *et al.* (1976). There was no significant difference in the proportions of cases in each diagnostic category in the three survey areas in 1961, but in 1981 a significant difference was apparent ($\chi^2$ 9.7, $P<0.05$). However, the proportion of clinically definite patients was very similar (c. 70%) in all three cities and the difference between them was due to there being relatively fewer probable and more possible cases in Perth than in either Newcastle or Hobart. Furthermore, there was no significant difference between the three cities combined in the distribution of diagnostic categories in 1981 as compared to 1961 ($\chi^2$ 2.9, $0.1<P<0.5$).

### *Prevalence*

There was a significant increase in the age-standardized prevalence rate in each city between 1961 and 1981 (Perth and Hobart $P<0.001$; Newcastle $P<0.01$) (fig. 1). Crude (Table 3) and age-standardized (Table 4) prevalence rates were not appreciably different. The increase in prevalence was more apparent in females in

TABLE 3. NO OF PATIENTS AND CRUDE PREVALENCE RATE OF MS BY DIAGNOSTIC CATEGORY IN EACH OF THE 3 CITIES IN 1961 AND 1981

| | *Census populations* | | *Definite* | | *Definite and probable* | | *All cases* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *City* | *1961* | *1981* | *1961* | | *1981* | | *1961* | | *1981* | | *1961* | | *1981* | |
| | | | *n* | *Prev* | *n* | *Prev* | *n* | *Prev* | *n* | *Prev* | *n* | *Prev* | *n* | *Prev* |
| Perth | 420,133 | 898,918 | 62 | 14.8 | 184 | 20.5 | 74 | 17.6 | 218 | 24.3 | 83 | 19.8 | 264 | 29.4 |
| Newcastle | 142,574 | 135,207 | 21 | 14.7 | 35 | 25.9 | 25 | 17.5 | 46 | 34.0 | 28 | 19.6 | 51 | 37.7 |
| Hobart | 115,932 | 168,363 | 25 | 21.6 | 91 | 54.0 | 33 | 28.5 | 115 | 68.3 | 37 | 31.9 | 125 | 74.2 |

n = number; Prev = prevalence rate /100,000 of population.

TABLE 4 AGE-STANDARDIZED PREVALENCE RATES PER 100,000 OF POPULATION BY SEX AND FOR ALL PERSONS IN EACH OF THE THREE CITIES IN 1961 AND 1981*

| | *Males* | | *Females* | | *All persons* | |
|---|---|---|---|---|---|---|
| *City* | *1961* | *1981* | *1961* | *1981* | *1961* | *1981* |
| Perth | 12.3 | 16.0 | 26.0 | 43.6 | 19.5 | 29.9 |
| Newcastle | 16.5 | 24.6 | 19.9 | 48.1 | 18.2 | 36.5 |
| Hobart | 17.9 | 52.6 | 50.2 | 96.4 | 34.5 | 75.6 |

* The data were age-standardized to the 1981 Australian population

both Perth and Newcastle while the converse was true in Hobart. This was reflected in an alteration of the female:male prevalence ratios in Perth from 2.3:1 to 2.9:1, in Newcastle from 1.5:1 to 2.0:1 and in Hobart from 2.1:1 to 1.9:1 in 1961 and 1981, respectively. However, there was no significant difference in the sex ratios between the survey areas in either 1961 ($\chi^2$ 2.5, $0.1 < P < 0.5$) or 1981 ($\chi^2$ 3.6, $0.1 < P < 0.5$).

The relationship between increasing south latitude and increasing prevalence rate found in 1961 was again seen in 1981 (fig. 1), there being a significant linear trend between these two variables in both 1961 ($P < 0.02$) and 1981 ($P < 0.001$). It should be noted that, because of the larger number of cases ascertained in the 1981 survey, the relationship was statistically much stronger in 1981 than in 1961.

Age-specific prevalence rates in 1981 are shown in Table 5 and fig. 2. In Perth and Newcastle the prevalence curves rose to clearcut peaks in the sixth decade for both sexes in the former city and in the fifth decade for both sexes in the latter. In Hobart the prevalence curves showed less clearcut peaks in both sexes with little change in prevalence between the fourth and sixth decades in males (maximum prevalence in sixth decade) and between the fifth and seventh decade in females (maximum prevalence in seventh decade). A comparison of age-specific prevalence rates for all persons in each city in 1961 and 1981 (fig. 3) showed that from the fourth decade of life onwards prevalence was notably higher in each city in 1981. Of particular interest was the rise in each city of the prevalence rate of patients in

TABLE 5 AGE-SPECIFIC PREVALENCE RATES FOR 1981 PATIENTS (ALL CATEGORIES) BY SEX AND FOR ALL PERSONS IN EACH CITY*

| | *Males* | | | *Females* | | | *All persons* | | |
|---|---|---|---|---|---|---|---|---|---|
| *Age group (yrs)* | *n* | *Pop. at risk* | *Prev / 100,000* | *n* | *Pop at risk* | *Prev / 100,000* | *n* | *Pop at risk* | *Prev / 100,000* |
| Perth | | | | | | | | | |
| 0–9 | 0 | 73004 | — | 0 | 69427 | — | 0 | 142431 | — |
| 10–19 | 0 | 84019 | — | 3 | 81858 | 3.7 | 3 | 165877 | 1.8 |
| 20–29 | 2 | 75025 | 2.7 | 17 | 78170 | 21.7 | 19 | 153195 | 12.4 |
| 30–39 | 15 | 68738 | 21.8 | 57 | 69133 | 82.4 | 72 | 137871 | 52.2 |
| 40–49 | 18 | 49468 | 36.4 | 41 | 49012 | 83.7 | 59 | 98480 | 59.9 |
| 50–59 | 19 | 42793 | 44.4* | 44 | 42217 | 104.2** | 63 | 85010 | 74.1** |
| 60–69 | 9 | 28349 | 31.7 | 27 | 33332 | 81.0 | 36 | 61681 | 58.4 |
| 70+ | 5 | 21451 | 23.3 | 7 | 32922 | 21.3 | 12 | 54373 | 22.1 |
| Total | 68 | 442847 | 15.4<br>(16.0) | 196 | 456071 | 43.0<br>(43.6) | 264 | 898918 | 29.4<br>(29.9) |
| Newcastle | | | | | | | | | |
| 0–9 | 0 | 8552 | — | 0 | 8382 | — | 0 | 16934 | — |
| 10–19 | 0 | 11210 | — | 1 | 10772 | 9.3 | 1 | 21982 | 4.5 |
| 20–29 | 3 | 12402 | 24.2 | 3 | 11147 | 26.9 | 6 | 23549 | 25.5 |
| 30–39 | 4 | 8367 | 47.8 | 7 | 8081 | 86.6 | 11 | 16448 | 66.9 |
| 40–49 | 4 | 6829 | 58.6** | 9 | 6878 | 130.9** | 13 | 13707 | 94.8** |
| 50–59 | 4 | 8419 | 47.5 | 7 | 8576 | 81.6 | 11 | 16995 | 64.7 |
| 60–69 | 2 | 6515 | 30.7 | 6 | 7674 | 78.2 | 8 | 14219 | 56.3 |
| 70+ | 0 | 4254 | — | 1 | 7119 | 14.0 | 1 | 11373 | 8.8 |
| Total | 17 | 66548 | 25.5<br>(24.6) | 34 | 68629 | 49.5<br>(48.1) | 51 | 135207 | 37.7<br>(36.5) |
| Hobart | | | | | | | | | |
| 0–9 | 0 | 13701 | — | 0 | 13106 | — | 0 | 26809 | — |
| 10–19 | 0 | 15615 | — | 1 | 15156 | 6.6 | 1 | 30771 | 3.2 |
| 20–29 | 7 | 14380 | 48.7 | 6 | 14731 | 40.7 | 13 | 29111 | 44.7 |
| 30–39 | 13 | 11893 | 109.3 | 19 | 12019 | 158.1 | 32 | 23912 | 133.8 |
| 40–49 | 9 | 8510 | 105.8 | 17 | 8540 | 199.1 | 26 | 17050 | 152.5 |
| 50–59 | 10 | 8498 | 117.7** | 18 | 8499 | 211.8 | 28 | 16997 | 164.7** |
| 60–69 | 4 | 6096 | 65.6 | 15 | 6972 | 215.1** | 19 | 13068 | 145.4 |
| 70+ | 0 | 4027 | — | 6 | 6618 | 90.7 | 6 | 10645 | 56.4 |
| Total | 43 | 82720 | 52.0<br>(52.6) | 82 | 85641 | 95.7<br>(96.4) | 125 | 168363 | 74.2<br>(75.6) |

* Prevalence rates in parentheses are age-standardized to the 1981 Australian population. ** Maximum age-specific prevalence rate n = no of cases, Pop. = population, Prev. = prevalence

the seventh decade of life and beyond. Table 6 indicates that whereas the percentage of people over the age of 60 yrs in the general population in each city showed at most a modest increase between the two surveys, the percentage of MS cases in that age bracket was considerably greater in 1981. In the three cities combined there had been a 305% rise in the proportion of MS patients but only a 6% rise in the proportion of the general population in this age bracket between the two surveys. Despite this finding, the peak age-specific prevalence rate showed no change for all persons in Perth and Newcastle, remaining in the sixth and fifth decades, respectively, while in Hobart the peak assumed a broader contour in 1981 and shifted from the fifth to the sixth decade.

The crude prevalence rates of MS in overseas born patients were higher than in

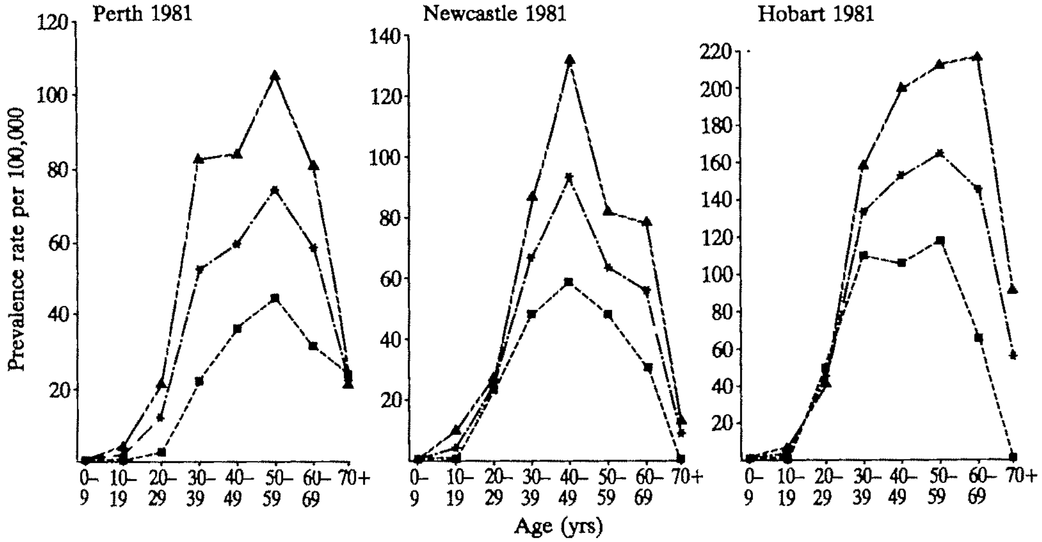

FIG. 2. Age-specific prevalence rates by sex and for all persons in each city in 1981. Females (triangles), males (squares), persons (asterisks)

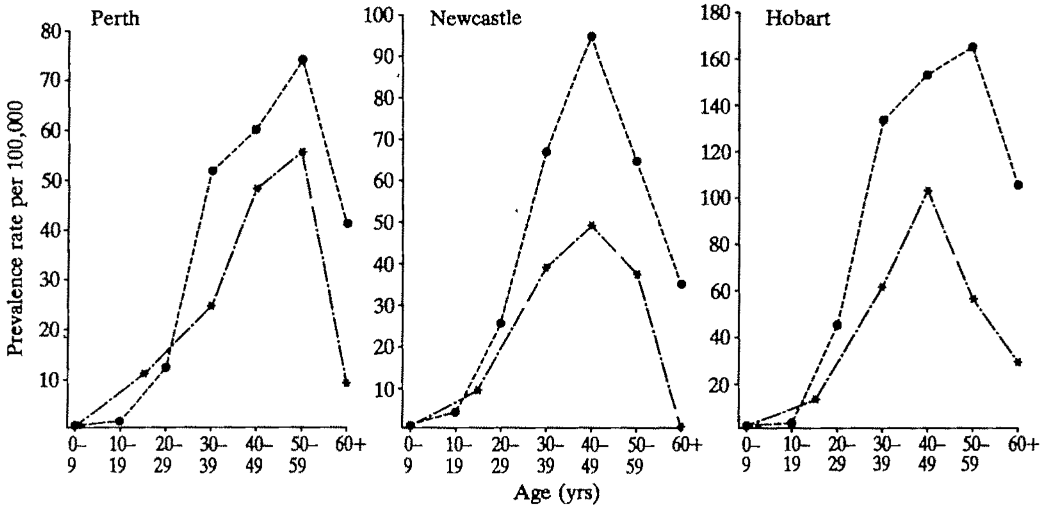

FIG 3. Comparison between age-specific prevalence rates (all persons) in 1961 and 1981 in each city 1981 (circles), 1961 (asterisks)

their Australian born equivalents (Table 7). However, because the age structure of the immigrant population was quite different to that of the Australian born population, being weighted towards the older age groups, much of the difference was removed by age-standardization of the prevalence rates (Table 8). In fact only in Hobart was the age-standardized prevalence rate of overseas born patients significantly higher ($P<0.01$) than in their Australian born equivalents; it was also noted to be significantly higher ($P<0.001$) than the equivalent rate for overseas

TABLE 6 COMPARISON OF THE PERCENTAGES OF THE TOTAL POPULATION AND OF MS PATIENTS OVER 60 YEARS OF AGE IN 1961 AND 1981

| *Over 60 yrs of age* | *1961* | | *1981* | |
|---|---|---|---|---|
| | *% total population* | *% MS cases* | *% total population* | *% MS cases* |
| Perth | 12.8 | 6.0 | 12.9 | 18.2 |
| Newcastle | 13.5 | 0.0 | 18.9 | 17.6 |
| Hobart | 11.8 | 10.8 | 14.1 | 20.0 |
| 3 cities | 13.0 | 6.1 | 13.8 | 18.6 |

TABLE 7 CRUDE AND AGE-STANDARDIZED PREVALENCE RATES FOR AUSTRALIAN AND OVERSEAS BORN PATIENTS (ALL DIAGNOSTIC CATEGORIES) IN 1981*

| | *Prevalence rate per 100,000* | | | |
|---|---|---|---|---|
| | *Australian born* | | *Overseas born* | |
| *City* | *Crude* | *Standardized* | *Crude* | *Standardized* |
| Perth | 22.8 | 27.6 | 43.6 | 33.0 |
| Newcastle | 37.2 | 38.1 | 41.7 | 28.9 |
| Hobart | 63.9 | 69.7 | 146.4 | 102.9 |

*The 1981 Australian population was used as the standard population

TABLE 8 COMPARISON OF ACTUAL AND EXPECTED CONTRIBUTIONS TO MS PREVALENCE BY OVERSEAS BORN PATIENTS IN 1961 AND 1981

| | *1961* | | *1981* | |
|---|---|---|---|---|
| *Overseas born* | *% total population* | *% MS cases* | *% total population* | *% MS cases* |
| Perth | 23.9 | 25.3 | 31.6 | 46.6 |
| Newcastle | 11.7 | 10.7 | 12.4 | 13.7 |
| Hobart | 12.1 | 10.8 | 12.6 | 24.8 |

born patients in either Perth or Newcastle. A comparison of the contribution by overseas born patients to the MS population in each city in 1961 and 1981 is seen in Table 8. Whereas in 1961 the actual contribution by overseas born patients was much as expected in each city it is clear that in 1981 their contribution to the MS populations in Perth and Hobart far exceeded expectations based on their contribution to the general population; this increase was significant in both cities (Perth $P<0.01$; Hobart $P<0.001$). In Newcastle, however, there had been only a minor increase in this respect since 1961 and the change was not significant.

In each city most immigrants came from the UK and Ireland (Perth 53.6%;

TABLE 9 BIRTHPLACE OF OVERSEAS BORN PATIENTS WITH MS IN 1981

| *Birthplace of overseas born patients* | *Perth* | *Newcastle* | *Hobart* | *3 cities* |
|---|---|---|---|---|
| UK and Ireland | 71.6% | 42.9% | 71.0% | 70.2% |
| Rest of Europe | 18.7% | 57.1% | 19.4% | 20.5% |
| USA and Canada | 4.1% | — | 6.4% | 4.3% |
| New Zealand | 2.4% | — | — | 1.9% |
| India and Pakistan | 2.4% | — | 3.2% | 2.5% |
| China | 0.8% | — | — | 0.6% |

TABLE 10 AGE-STANDARDIZED PREVALENCE RATES FOR AUSTRALIAN AND ENGLISH BORN PATIENTS (ALL DIAGNOSTIC CATEGORIES) IN PERTH AND HOBART IN 1981

| | *Age-standardized prevalence per 100,000* | | | |
|---|---|---|---|---|
| | *Australian born* | | *English born* | |
| *City* | *Rate* | *95% CI* | *Rate* | *95% CI* |
| Perth | 27.6 | 23.3–32.7 | 44.1 | 34.3– 56.1 |
| Hobart | 69.7 | 56.3–85.0 | 141.1 | 82.1–225.8 |

CI = Confidence Interval The data were age-standardized to the 1981 Australian population

TABLE 11 AGE AT IMMIGRATION OF OVERSEAS BORN POPULATION FROM ALL COUNTRIES OF ORIGIN AND FROM ENGLAND ALONE IN PERTH AND HOBART IN 1981

| | *Age at immigration of overseas born population* | | | | | |
|---|---|---|---|---|---|---|
| | *All countries* | | | *England* | | |
| *City* | *Pop* | *<15* | *>15* | *Pop.* | *<15* | *>15* |
| Perth | 284,444 | 29.5% | 70.5% | 125,594 | 32.0% | 68.0% |
| Hobart | 21,187 | 28.7% | 71.3% | 8,808 | 31.7% | 68.3% |

Pop = population, <15 and >15 = less than and more than 15 yrs of age

Newcastle 37.4%; Hobart 51.0%), with similar contributions in each city from the 5 individual countries concerned (England: Perth 82.3%, Newcastle 70.2%, Hobart 81.6%; Scotland: Perth 10.8%, Newcastle 20.9%, Hobart 11.6%; Wales: Perth 2.1%, Newcastle 4.6%, Hobart 2.4%; Northern Ireland: Perth 1.4%, Newcastle 1.5%, Hobart 1.5%; Eire: Perth 3.4%, Newcastle 2.8%, Hobart 2.9%). Most of the overseas born patients in 1981 also originated from the UK and Ireland (Table 9). Onset of disease after migration into Australia occurred in 88/123 (71.5%), 7/7 (100%) and 23/31 (74.2%) of immigrants to Perth, Newcastle and Hobart, respectively. England was the only country of origin which provided sufficient numbers of patients in either Perth (69) or Hobart (17) for the separate calculation of prevalence rates (Table 10). It can be seen that the age-standardized prevalence rate of English born patients was significantly higher than their Australian born equivalents in both cities (in Hobart, the confidence intervals slightly overlap but the difference was still significant at $P<0.01$). Furthermore, the prevalence rates for both Australian and English born patients were significantly higher in Hobart than in Perth. A statistically higher prevalence rate for overseas born patients as a whole was also found in Hobart than in Perth (*see* above). Data obtained from the ABS showed that there was no significant difference in the distribution of countries of origin of the overseas population in Perth as compared with Hobart with regard to their risk status for MS. Furthermore, the overseas born (all countries of origin) and English born populations from which these patients came showed no significant differences in age at migration (Table 11) or duration of residence in Australia profiles in Perth as compared with Hobart.

The proportion of Australian born patients in each city who had travelled overseas to countries known to be 'high risk' for MS prior to disease onset, was similarly small, this occurring in only 7 (5.0%), 2 (4.5%) and 5 (5.3%) instances in Perth, Newcastle and Hobart, respectively. The countries concerned were England (9 instances), New Zealand (4 instances) and Scotland (1 instance).

### *Incidence*

Incidence rates per 100,000 person years for the decades 1950 to 1959 and mid-1971 to mid-1981 are compared in Table 12. Age-standardized incidence was higher both in Newcastle and Hobart in the more recent decade but the rate in Perth remained much the same. However, none of the changes was significant (Perth $P>0.3$; Newcastle and Hobart $0.05<P<0.1$). Age-standardization of the rates for the more recent decade did not substantially alter the crude figures. In 1961, the crude incidence rate in Hobart was significantly higher than in Perth ($P<0.02$) but not in comparison with Newcastle ($0.05<P<0.1$) in view of the small numbers involved; the age structure of the respective denominator populations used to calculate these rates was very similar. In 1981, the age-standardized incidence rate of Hobart was significantly higher than in both Perth ($P<0.001$) and Newcastle ($P<0.05$); however, whereas in 1961 the incidence rates in Perth and Newcastle were essentially identical, in 1981 the rate in perth was significantly less than that

TABLE 12 INCIDENCE RATE PER 100,000 PERSON YEARS IN THE DECADES 1950–1959 AND MID-1971 TO MID-1981 IN EACH CITY*

| | *Cases with onset* | | *Census populations* | | *Average annual incidence* | |
|---|---|---|---|---|---|---|
| *City* | *1950–1959* | *1971–1981* | *1954* | *1976* | *1950–1959* | *1971–1981* |
| Perth | 41 | 106 | 348,647 | 805,748 | 1.2 | 1.3 (1.3) [1.3] |
| Newcastle | 17 | 29 | 137,428 | 138,719 | 1.2 | 2.1 (2.3) [2.3] |
| Hobart | 21 | 57 | 95,206 | 162,063 | 2.2 | 3.5 (3.7) [3.6] |

*The figures in ordinary and square parentheses for the 1971–1981 decade are the incidence rates after age-standardization to the 1981 Australian population and to the 1954 populations in each city respectively.

TABLE 13 AGE-SPECIFIC INCIDENCE RATES IN THE DECADE MID 1971 TO MID 1981 FOR PATIENTS (ALL CATEGORIES) BY SEX AND FOR ALL PERSONS IN EACH CITY*

| | *Males* | | | *Females* | | | *All persons* | | |
|---|---|---|---|---|---|---|---|---|---|
| *Age group (yrs)* | *n* | *Pop at risk* | *Inc / 100,000* | *n* | *Pop at risk* | *Inc / 100,000* | *n* | *Pop. at risk* | *Inc./ 100,000* |
| Perth | | | | | | | | | |
| 0–9 | 0 | 73726 | — | 1 | 69791 | 0.14 | 1 | 142517 | 0.07 |
| 10–19 | 0 | 78490 | — | 7 | 76337 | 0.92 | 7 | 154827 | 0.45 |
| 20–29 | 5 | 69341 | 0.72 | 26 | 70817 | 3.67 | 31 | 140158 | 2.21 |
| 30–39 | 10 | 53042 | 1.88** | 25 | 53048 | 4.71** | 35 | 106090 | 3.30** |
| 40–49 | 6 | 45077 | 1.33 | 19 | 43843 | 4.33 | 25 | 88920 | 2.81 |
| 50–59 | 1 | 36209 | 0.28 | 5 | 36710 | 1.36 | 6 | 72919 | 0.82 |
| 60–69 | 0 | 25929 | — | 1 | 30145 | 0.33 | 1 | 56074 | 0.18 |
| 70+ | 0 | 16789 | — | 0 | 26454 | — | 0 | 43243 | — |
| Total | 22 | 398603 | 0.55 | 84 | 407145 | 2.06 | 106 | 805748 | 1.32 |
| | | | (0.57) | | | (2.12) | | | (1.35) |
| Newcastle | | | | | | | | | |
| 0–9 | 0 | 10030 | — | 0 | 9668 | — | 0 | 19697 | — |
| 10–19 | 2 | 12343 | 1.62 | 2 | 12058 | 1.66 | 4 | 24402 | 1.64 |
| 20–29 | 6 | 11445 | 5.24** | 6 | 10640 | 5.64 | 12 | 22085 | 5.43** |
| 30–39 | 2 | 7577 | 2.64 | 5 | 7433 | 6.73** | 7 | 15010 | 4.66 |
| 40–49 | 4 | 7848 | 5.09 | 2 | 7986 | 2.50 | 6 | 15833 | 3.79 |
| 50–59 | 0 | 8816 | — | 0 | 8922 | — | 0 | 17738 | — |
| 60–69 | 0 | 6400 | — | 0 | 7309 | — | 0 | 13708 | — |
| 70+ | 0 | 3850 | — | 0 | 6397 | — | 0 | 10246 | — |
| Total | 14 | 68309 | 2.05 | 15 | 70413 | 2.13 | 29 | 138719 | 2.09 |
| | | | (2.09) | | | (2.50) | | | (2.29) |
| Hobart | | | | | | | | | |
| 0–9 | 0 | 14266 | — | 0 | 13785 | — | 0 | 28050 | — |
| 10–19 | 3 | 16360 | 1.83 | 5 | 16168 | 3.09 | 8 | 32529 | 2.46 |
| 20–29 | 9 | 14166 | 6.35 | 7 | 13815 | 5.07 | 16 | 27981 | 5.72 |
| 30–39 | 10 | 9870 | 10.13** | 9 | 9887 | 9.10** | 19 | 19758 | 9.62** |
| 40–49 | 3 | 8618 | 3.48 | 4 | 8355 | 4.79 | 7 | 16972 | 4.12 |
| 50–59 | 1 | 7893 | 1.27 | 4 | 8318 | 4.81 | 5 | 16210 | 3.08 |
| 60–69 | 0 | 5590 | — | 2 | 6133 | 3.26 | 2 | 11724 | 1.71 |
| 70+ | 0 | 3191 | — | 0 | 5648 | — | 0 | 8839 | — |
| Total | 26 | 79954 | 3.25 | 31 | 82109 | 3.77 | 57 | 162063 | 3.52 |
| | | | (3.39) | | | (3.99) | | | (3.70) |

* Incidence rates in parentheses are age-standardized to the 1981 Australian population ** Maximum age-specific incidence rate n = no. of cases, Pop = population, Inc = Incidence.

of Newcastle ($P < 0.05$). This finding most likely relates to underascertainment of incidence cases in Perth (*see* below).

The peak age-specific incidence rate occurred in the fourth decade of life for both sexes in each city with the exception of the Newcastle males whose peak occurred in the third decade (Table 13; fig. 4). There was a significant difference in the female-male incidence ratios ($\chi^2$ 14.4, $P < 0.001$), with Perth showing a figure of 3.8:1 as compared to 1.2:1 in both Newcastle and Hobart suggesting underascertainment of male incidence cases in Perth.

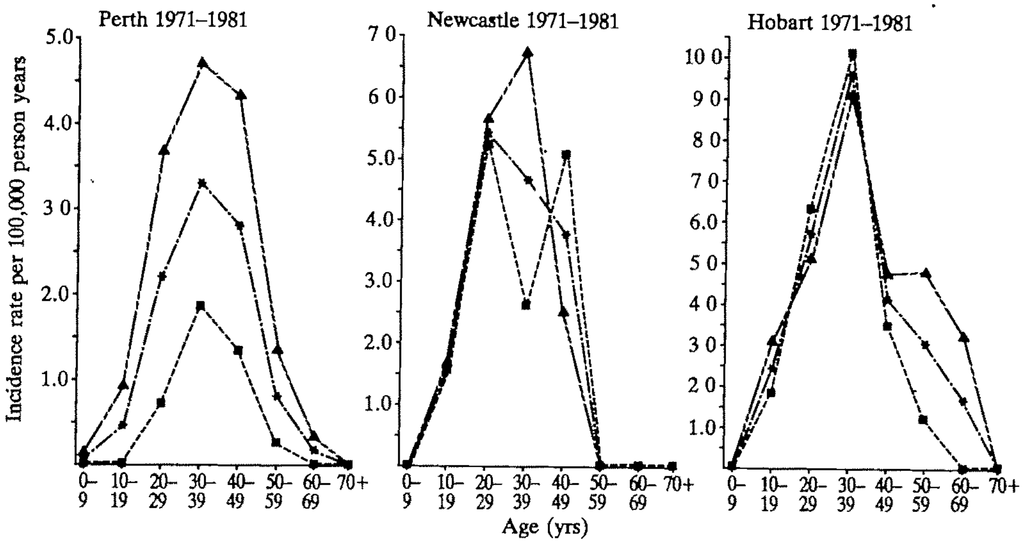

FIG 4. Age-specific incidence rates by sex and for all persons in each city in the decade mid-1971 to mid-1981 Symbols as for fig. 2

TABLE 14. CRUDE AND AGE-STANDARDIZED INCIDENCE RATES FOR AUSTRALIAN AND OVERSEAS BORN PATIENTS IN THE DECADE MID-1971 TO MID-1981*

*Incidence rate per 100,000*

| | *Australian born* | | *Overseas born* | |
|---|---|---|---|---|
| *City* | *Crude* | *Standardized* | *Crude* | *Standardized* |
| Perth | 1.11 | 1.28 | 1.77 | 1.54 |
| Newcastle | 2.14 | 2.38 | 1.76 | 1.57 |
| Hobart | 3.32 | 3.60 | 4.88 | 4.16 |

* The 1981 Australian population was used as the standard population.

As with prevalence, in Perth and Hobart crude incidence was higher amongst overseas born patients than in their Australian born equivalents but much of the difference was again removed by age-standardization of the figures (Table 14). In Newcastle crude incidence was higher amongst Australian born patients and this difference was exaggerated by age-standardization. However, there was no significant difference between the age-standardized incidence rates of Australian and overseas born patients in any of the cities. The contribution of overseas born patients to MS incidence in each of the three cities in the decade prior to prevalence day is shown in Table 15. As with prevalence (*see* Table 8) it can be seen that overseas born patients made a greater than expected contribution in Perth and Hobart but not in Newcastle.

TABLE 15 COMPARISON OF ACTUAL AND EXPECTED CONTRIBUTIONS TO MS INCIDENCE IN THE DECADE MID-1971 TO MID-1981 BY OVERSEAS BORN PATIENTS

| *Overseas born* | *% total population (1976 census)* | *% MS incidence cases 1971–1981* |
|---|---|---|
| Perth | 31.6 | 42.9 |
| Newcastle | 12.3 | 10.3 |
| Hobart | 12.7 | 17.5 |

## *Mortality*

Crude and age-standardized mortality rates per 100,000 person years for the half decade from mid-1976 to mid-1981 (direct method of data collection) were highest for Newcastle city (Table 16). This was an unexpected finding because gradients established by mortality data are generally reflected in similar prevalence gradients and thus the highest mortality rate would have been expected in Hobart. However, the mortality rate for the whole Newcastle statistical district (1981 census population 389,235) showed the expected relationship with the mortality rate in Hobart and its prevalence rate (crude: 36.5, age-standardized 36.1/100,000) was virtually identical with that of Newcastle city. This difference was most probably due to a concentration of terminally ill patients within Newcastle city itself because of better availability of facilities there to care for such patients. Support for this assumption comes from the fact that the mean Kurtzke disability score for the whole Newcastle statistical district in 1981 was 3.7 compared with 4.3 for Newcastle city alone.

TABLE 16 MORTALITY RATES PER 100,000 PERSON YEARS IN THE HALF-DECADE MID-1976 TO MID-1981 (DIRECT) AND IN THE DECADE 1971–1980 (INDIRECT) IN EACH SURVEY AREA

| | *Direct (survey)* | | *Indirect (ABS)* | |
|---|---|---|---|---|
| *Survey area* | *Deaths (mid 1976 to mid 1981)* | *Mortality rate* | *Deaths (1971 to 1980)* | *Mortality rate* |
| Perth | 6 | 0.14 (0.15) | — | — |
| Western Australia | 6 | 0.10 (0.11) | 40 | 0.36 |
| Newcastle City | 6 | 0.88 (0.72) | 9 | 0.65 |
| Newcastle stat. district | 10 | 0.53 (0.50) | 13 | 0.36 |
| Hobart | 5 | 0.61 (0.62) | 13 | 0.80 |

ABS = Australian Bureau of Statistics, stat = statistical. The figures in parentheses are the mortality rates after age-standardization to the 1981 Australian population

Mortality rates for the decade 1971–1980 calculated from figures provided by the ABS (indirect method of data collection) (Table 16) also showed the discrepancy between Newcastle city and the Newcastle statistical district. Unfortunately, ABS mortality figures are not available for the Perth statistical division but the figure for the State of Western Australia, the majority (c. 75%) of whose population resides in Perth, was noted to be essentially identical to that of the Newcastle statistical district and to be notably larger than the figure obtained for Perth or Western Australia by the direct method of data collection. Assuming that the mortality rate for the Newcastle statistical district is more representative than that of Newcastle city and given a mean latitude of 31°24′S for the 1976 populace of Western Australia (this was calculated from ABS data on the 1976 population distribution by statistical divisions) a statistically significant linear relationship ($P < 0.01$) between increasing south latitude and increasing mortality rates is seen which reflects the gradient observed for the prevalence rates (*see* above).

### *Clinical aspects*

The mean age at onset of all persons in 1981 was very similar in the 3 cities and showed little variation from the figures for all persons in 1961 (Table 17). However, the mean duration of disease on prevalence day was longer for all persons in each city in 1981 as compared with 1961 (Table 17).

TABLE 17 AGE AT ONSET AND DURATION OF DISEASE ON PREVALENCE DAY IN THE 3 CITIES BY SEX AND FOR ALL PERSONS IN 1961 AND 1981

| | *Mean age at onset of disease (yrs)* | | | | | | *Mean duration on prevalence day (yrs)* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Males* | | *Females* | | *Persons* | | *Males* | | *Females* | | *Persons* | |
| *City* | *1961* | *1981* | *1961* | *1981* | *1961* | *1981* | *1961* | *1981* | *1961* | *1981* | *1961* | *1981* |
| Perth | 34.0 | 33.4 | 32.8 | 31.3 | 33.2 | 31.9 | 10.6 | 15.7 | 10.3 | 13.9 | 10.4 | 14.4 |
| Newcastle | 26.7 | 28.9 | 32.2 | 30.8 | 29.6 | 30.1 | 15.3 | 15.0 | 8.7 | 15.8 | 11.8 | 15.5 |
| Hobart | 36.5 | 31.9 | 31.6 | 32.8 | 33.1 | 32.5 | 9.3 | 9.9 | 13.6 | 15.4 | 12.3 | 13.5 |
| 3 cities | | | | | 32.5 | 31.9 | | | | | 11.1 | 14.3 |

Comparison of the disability profiles of the patients in 1961 and 1981 is complicated by the fact that disability was assessed with different criteria on the two prevalence days. The Hyllested (1961) DSS (scores 0–6) was used in 1961 and the Kurtzke (1970) DSS (scores 0–10) in 1981. Table 18 shows that in 1961 the mean Hyllested scores were close to 3 in each area for all persons in all diagnostic categories whilst in 1981 the mean Kurtzke DSS scores in the equivalent patients were around 4. A score of 3 on the Hyllested scale indicates ‘moderately disabled with particular difficulties in walking; preferably two sticks out of doors or aided by helpers; leans on furniture when walking indoors; requires assistance for certain simple duties such as eating’; this is essentially equivalent to a score of 6 on the Kurtzke scale, this being defined as ‘assistance (canes, crutches, braces) required for walking’. In contrast a Kurtzke grade of 4 is defined as ‘relatively severe disability though fully ambulatory and able to be up and about for some 12 hours a day’. Thus the data suggest that the mean disability of patients in 1981 was less than in 1961.

TABLE 18 DEGREE OF DISABILITY ACCORDING TO THE HYLLESTED SCALE IN 1961 AND THE KURTZKE SCALE IN 1981 FOR PATIENTS (ALL CATEGORIES) BY SEX AND FOR ALL PERSONS IN EACH CITY AND IN THE 3 CITIES COMBINED (SCALES HYLLESTED 0–6, KURTZKE 0–10)

| | *1961* | | | *1981* | | |
|---|---|---|---|---|---|---|
| | *Mean Hyllested DSS* | | | *Mean Kurtzke DSS* | | |
| *City* | *M* | *F* | *Pers* | *M* | *F* | *Pers* |
| Perth | 2.6 | 2.9 | 2.8 | 4.0 | 3.4 | 3.6 |
| Newcastle | 2.5 | 3.3 | 2.9 | 3.3 | 4.7 | 4.3 |
| Hobart | 2.7 | 2.9 | 2.8 | 3.1 | 4.3 | 3.9 |
| 3 cities | 2.6 | 3.0 | 2.8 | 3.6 | 3.8 | 3.8 |

DSS = Disability Status Score, M = males, F = females; Pers = persons

## DISCUSSION

The 1961 survey of Perth, Newcastle and Hobart (McCall *et al.*, 1968), together with that of Sutherland *et al.* (1966) in Queensland in 1961, established a clear relationship in Australia between increasing latitude and increasing prevalence of MS, similar to the well documented general association between these variables in the northern hemisphere amongst white peoples of central and northern European origin (Kurtzke, 1983; Acheson, 1985). The present study has confirmed and strengthened this association for the southern half of continental Australia. Furthermore, in an equivalent follow-up study of Queensland (Hammond *et al.*, 1987), age-standardized prevalence rates of 11.8 and 21.0 per 100,000 were found above and below the Tropic of Capricorn, respectively ($P<0.001$), thus confirming that the gradient also holds for the northern half of the continent. The reproducibility of this prevalence gradient in sequential surveys separated by twenty years and the presence of medical facilities of a uniformly high standard across the continent make it very unlikely that this is an artefactual finding. Moreover, independent verification of the latitude gradient is apparent from an examination of mortality rates derived from data obtained from the ABS pertaining to Newcastle and Hobart (Table 16). Nevertheless, in view of the substantial immigration into Australia in recent years, the question arises as to whether some of the prevalence gradient may have resulted from an uneven distribution of these immigrants, most of whom came from the UK and Ireland. In a recent review, Swingler and Compston (1986) noted that susceptibility to MS varies considerably within the UK, being highest in Scotland, this difference probably relating in part to genetic factors. However, no substantial differences in the distribution of the individual countries of origin of migrants from the UK and Ireland were apparent between the three cities or, indeed, Queensland (Hammond *et al.*, 1987) in 1981. Furthermore, if, as suggested by Skegg *et al.* (1987), the proportion of names beginning with 'Mac' or 'Mc' in the telephone directories of each survey area is taken as a very crude index of Scottish ancestry in their respective total populations, there is no clear relationship with latitude. Thus the prevalence gradient within Australia argues strongly for the existence of an important environmental factor in the aetiology of MS.

Kurtzke (1983) has defined a high risk zone as one with a prevalence rate of 30 or more and the present study suggests that the southern part of australia below 32° south latitude falls into this category. A recent prevalence study of MS in Wellington, New Zealand (Miller *et al.*, 1986) which has an equivalent latitude (41°17′S) to Hobart (42°40′S), found a prevalence rate of 69 per 100,000 which is in close agreement with the rate in Hobart and confirms earlier studies in Wellington (Hornabrook, 1971) and Christchurch (latitude 43°33′S) (Cuningham, 1972) that New Zealand is also a high risk zone for MS. Hornabrook (1971) also compared hospital admission and mortality rates for three regions within New Zealand which spanned the latitudes 37°S to 47°S and found that both rates indicated increasing frequency of MS with increasing south latitude in that land. This frequency gradient has recently been confirmed in a regional epidemiological survey in the North and South Islands of New Zealand (Skegg *et al.*, 1987) although, in contrast to the present study, there was a possibility that this finding was partly due to genetic factors.

Unfortunately, apart from Australia and New Zealand, the distribution of MS in the southern hemisphere remains largely unknown. No formal epidemiological studies of MS have been performed in South America and estimates of prevalence there rely on ratios of cases of MS to cases of amyotrophic lateral sclerosis. These were provided for Caracas, Venezuela by Borges-Iturriza and Briceno (1977) and for several other regions of South America by Christensen (1975) from a survey of neurologists by questionnaire. Kurtzke's (1980) interpretation of these data indicates that there may be a similar gradient of MS prevalence with latitude in that continent. Similarly there have been few epidemiological studies of MS in Africa. Dean (1967) found a crude prevalence of 9.1 per 100,000 in native born white South Africans, a figure similar to the rates found in Queensland (Sutherland *et al.*, 1966) at that time.

The second major finding of this study is that age-standardized prevalence rates in all three cities were significantly higher in 1981 than in 1961 (*see* Table 4). In a recent review, Acheson (1985) stated that an almost universal rule concerning prevalence studies of MS is that later studies of the same area show higher rates than do earlier studies. The major question which arises from the observation of such an increase is whether it indicates a true increase in disease incidence or whether it is explicable by other means. The question is of considerable importance as the former explanation necessarily implies that the influence of exogenous factors relevant to the causation of MS is increasing. Poskanzer *et al.* (1980) have stated that increased prevalence over time may be due to any combination of five factors: an increase in incidence of the disease; an increase in survival (duration of the disease); more complete ascertainment of cases on restudy; changes in the age structure of the population; and differential migration of patients compared with the general population. Two potentially important influences on the completeness of ascertainment on restudy are increased awareness of the less severe forms of the disease (Acheson, 1985) and the existence of modern laboratory diagnostic investigations which, even if they are not used in the classification of patients (as in this study), may nevertheless lead to an increase in referrals of patients suspected of having MS (Lauer and Firnhaber, 1985).

In the current study, despite a uniform approach to case ascertainment and equivalent standards of medical facilities in each area, there were considerable differences between the areas in the proportions of cases notified by some sources (Table 1). Overall the results suggest that case finding was more complete in Newcastle and Hobart than in Perth, the reverse of the conclusions drawn for the 1961 data (McCall *et al.*, 1968). Improvement in case ascertainment is likely to have played an important part in increasing prevalence in Newcastle in 1981 since there was an increase in the average number of sources reporting each case from 2 in 1961 to 3.2 in 1981. This change was mainly due to the considerable expansion of neurological services there between the two surveys which is reflected in the fact that only 15% of cases were notified by neurologists in 1961 compared with 84% in 1981. In Hobart the increase in the average number of sources reporting each case from 2.5 in 1961 to 2.9 in 1981 indicates that the influence of improved case ascertainment on increased prevalence there is likely to have been modest although a degree of underascertainment was suspected in that city in 1961 (McCall *et al.*, 1968; Cuningham, 1972). In Perth the decrease in the average number of sources reporting each case from 3 in 1961 to 2.3 in 1981 suggests that case ascertainment was less complete in the current survey. This is given further credence by the discrepancy in Perth between the mortality rates calculated from figures obtained by the direct and indirect methods of data collection (Table 16). The incidence data further suggested that underascertainment was predominant in males. The most likely reason for comparative underascertainment there in the current survey is change in population size. Between 1961 and 1981 Perth more than doubled its population; in 1981 it was 5.3 and 6.6 times larger than the populations in Hobart and Newcastle respectively (Table 3). Thus comparative under-reporting of cases in Perth is not altogether surprising because case finding is usually more complete in surveys of small rather than large populations resulting in the reporting of higher incidence and prevalence figures in the former (Kurland *et al.*, 1965; Acheson, 1985). Nowhere is this better exemplified than by the recent experience in Italy (*see* Acheson, 1985).

Two other factors worthy of mention in regard to case ascertainment in this study are the duration of case collection and the role of the MS Societies. On average, prevalence cases were collected over a 12 month period in the 1961 study whereas in the current survey the duration of case collection was about twice as long in each survey area. Furthermore, in the period between the two surveys, the MS Societies subserving Newcastle and Hobart had expanded considerably and in

Perth a MS Society branch had been established, there having been no such organisation there in 1961. Both these factors are clearly likely to have contributed to improved ascertainment in Newcastle and Hobart, and to offsetting the negative influence of population growth on ascertainment in Perth.

Lauer and Firnhaber (1985) have pointed out that modern laboratory diagnostic investigations may potentially influence prevalence rates by bringing patients suspected of having MS to the attention of the surveyor even if they are not used to classify cases as in this study. Inclusion of a greater proportion of such patients who would mostly be at an early stage in the evolution of their disease would have been expected to decrease the mean duration between disease onset and prevalence day. However, Table 17 shows that the opposite was the case. Similarly, because such investigations are of greater value in the diagnostically less certain categories of MS, a positive contribution from them to increased prevalence in this study might have been expected to increase the proportions of the less certain diagnostic categories at the expense of the clinically definite category. However, Table 2 shows that clinically definite cases were similarly distributed in each city in both surveys accounting for between 65% and 73% of cases in 1961 and between 69% and 73% of cases in 1981. Furthermore, there was no significant difference in the distribution of diagnostic categories in the three cities combined between the two surveys. Thus the availability of modern diagnostic investigations does not seem to have been an influential factor in this study.

Acheson (1985) has stated that increased recognition of the less severely disabled cases may contribute to an increase in prevalence over time. If this had contributed to increased prevalence in the present study then a decrease in mean disability would have been expected for the 1981 patients. Assessment of the influence of this factor in this study was complicated by the fact that disability was assessed with the Hyllested (1961) scale in 1961 and the Kurtzke (1970) scale in 1981. Nevertheless, the data (Table 18) do support a fall in mean disability in 1981 in each city and, by implication, a contribution to the increased prevalence rate in each city from a better recognition of the less severely disabled categories of MS patients.

There are three lines of evidence which suggest that an increase in survival (duration of the disease) has contributed to the increase in prevalence in 1981 in each of the three cities. First, the mortality rate from MS derived from ABS data has fallen over the past three decades in the States of New South Wales and Tasmania, although remaining essentially stable in Western Australia. The crude mortality rates per 100,000 person years for the decades 1950–1959 and 1971–1980 were 0.64 and 0.46 respectively in New South Wales, 1.11 and 0.79 respectively in Tasmania, and 0.33 and 0.36 respectively in Western Australia. Secondly, while mean age at onset was much the same in the two surveys, the mean duration of disease had increased in all three cities by 1981 (Table 17). This was most pronounced in Perth and Newcastle but was more modest in Hobart. It has been estimated that mean life expectancy in MS is twice the disease duration from onset to prevalence day (Poskanzer *et al.*, 1963). For the three cities combined this would indicate that mean survival has increased from around 22 yrs in 1961 to around 29 yrs in 1981. Thirdly, analysis of age-specific prevalence rates shows that whilst there had been little or no change in the position of the peak rates for all persons in each area, the rates for patients in the seventh decade of life and beyond were much higher in 1981 (Table 5, fig. 3). In other words, there were proportionately more elderly patients in 1981 than in 1961. Table 6 shows that while there was only a slight increase in the proportion of the general population over the age of 60 yrs between the two surveys, the proportion of patients in this age bracket had increased by three times for the three cities combined.

Changes in the age structure of a population do not influence the prevalence of a relatively uncommon disease like MS unless the changes are marked (Taylor *et al.*, 1980). Because MS prevalence rates generally peak in the fifth or sixth decades of life a substantial shift in the population age structure to favour older age groups would increase the overall crude prevalence of the disease. Similarly, a substantial increase of the proportion of people within a population in the first two decades of life would decrease overall MS crude prevalence, and this is thought to have been the main reason for the recently described decrease in prevalence in Western Poland (Wender *et al.*, 1985). However, ABS data show that there was very little change in population age structure between the two surveys in any of the three cities in the present study. Moreover, the potential influence of this factor has been obviated in the present study by the age-standardization of prevalence rates.

Immigration has made an important contribution to increasing overall population size in Australia between the two surveys. Since the majority of these immigrants come from areas of Europe which are high risk zones for MS, they also represented a possible means by which prevalence (and incidence—*see* below) could have increased with time. In each city in 1981, crude prevalence rates of MS in overseas born patients were higher than in their Australian born equivalents (Table 7) but, because the age distribution of the immigrant population was weighted towards the older age groups, much of that difference was removed by age-standardization of the prevalence rates. In fact, only in Hobart was the age-standardized prevalence rate significantly higher amongst overseas born patients than in their Australian born equivalents. However, with respect to the increase in prevalence between the two surveys, it is the change in the contribution from overseas born patients (Table 8) which is the more important consideration. In 1961 their contribution to the MS data base was much as would be expected from their contribution to the overall population whereas it might have been expected to have been higher, given that the majority of them came from the UK which is known to be a high risk zone for MS (Kurtzke, 1975, 1980). This finding was thought to be due to the stringent immigrant screening policy of the day (McCall *et al.*, 1968). However, by 1981 there had been a substantial and significant increase in the proportion of overseas born patients in terms of their contribution to the overall population in both Perth ($P<0.01$) and Hobart ($P<0.001$), while in

Newcastle there had been only a minor increase in this respect since 1961 and the change was not significant. Since the great majority of the overseas born patients in 1981 came from the UK, Ireland and other areas of Europe which are high risk zones for MS (Table 9), it seems clear that differential immigration of an overseas born population at a higher risk of developing MS than the indigenous population contributed to the increase in prevalence in 1981 in Perth and Hobart.

Studies of migrant populations relating alterations in risk of acquiring MS to age at migration (Alter *et al.*, 1966, 1971, 1978; Dean and Kurtzke, 1971; Detels *et al.*, 1978) have suggested that the critical age is about 15 yrs. Thus populations migrating from high to low risk zones acquired the low risk of the country to which they had migrated if migration occurred before the age of 15 but took their high risk with them if migration occurred after the age of 15. Studies of ages of maximal cohabitation amongst sibling pairs, both of whom subsequently developed MS (Schapira *et al.*, 1963), and of maximal space/time clustering of MS cases in certain geographic regions in the years prior to their disease becoming clinically overt (Kurtzke, 1965), have also suggested that the age of acquisition of MS is generally between 10 and 15 yrs. However, analysis of the Faroe MS data (Kurtzke and Hyllested, 1979, 1986; Fischman, 1981) has suggested the age range of acquisition of MS may be considerably wider, and our data may lend support to this contention. The distribution of countries of origin (mostly high risk for MS) of the overseas born population in Perth and Hobart in 1981 were very similar; in particular, the proportion of migrants from each of the five constituent countries of the UK and Ireland, which together provided the majority of migrants in each city, was very similar. Furthermore, the age at migration (Table 11) and duration of residency profiles of the overseas born (all countries of origin) and English born populations in Perth and Hobart show no significant differences; migration over the age of 15 yrs occurred in about 70% of the overseas born (all countries of origin) and English born populations in both cities. It would therefore be expected that the prevalence rate of MS amongst the immigrant population would be similar in the two cities if all patients with MS acquire their disease by the age of 15. The prevalence rate in Hobart would at most be expected to be no more than 30% higher than in Perth (assuming the extreme situation in which the population migrating under the age of 15 to Hobart continued to develop MS at much the same rate as their counterparts who migrated over the age of 15, while no cases of MS arose in those migrating under the age of 15 to Perth). However, the age-standardized prevalence rate for overseas born patients (all countries of origin) and English born patients was approximately three times higher in Hobart than in Perth, this being a highly significant difference in each case. While under-ascertainment of overseas born patients in Perth might have partly accounted for this finding, it is unlikely that differences of this magnitude could be totally accounted for in this way. Two alternative explanations suggest themselves: first, if risk of acquisition of MS is totally decided by the age of 15, then clinical expression of the disease has been modified by environmental factors prevalent in

P25695

Perth but not in Hobart; secondly, the risk of acquisition of MS is not entirely decided by the age of 15 but rather spans a much wider age range, as suggested by the Faroe data. With regard to the second explanation, it is clear that the English born migrant population have brought with them at least some of their high risk status for MS as evidenced by their significantly higher prevalence rates in both cities in comparison to the indigenous population (Table 10) who are largely derived from the same stock. Indeed, in Hobart the age-standardized rate amongst English born migrants (Table 10) is of a similar order considering its wide 95% confidence intervals to crude rates for all cases found in West Yorkshire in northern England (127/100,000; 95% CI 79–194) (McCoubrie and Shuttleworth, 1978) and more recently in Sutton, a borough south of London in southern England (115/100,000; 95% CI 100–133) (Williams and McKeran, 1986).

Differences in the proportion of Australian born patients in each city who had periods of residence in countries of the northern hemisphere known to be high risk for MS prior to disease onset, with the consequent theoretical risk of having acquired the disease overseas rather than locally, could potentially have influenced the respective prevalence rates. However, there was no significant difference between the cities in this respect in 1981 with only approximately 5% of Australian born patients being exposed to such a risk.

A comparison of average annual incidence rates over a 10 yr period (Table 12) prior to each survey period showed that in Perth the rate had remained essentially stable while in Newcastle and Hobart the rates had increased, but the incidence change with time was not significant in any city. In 1981 the age-standardized incidence rate was significantly higher in Hobart than in Perth or Newcastle, a finding that reflects the relationship with latitude found with both the prevalence and mortality rates. However, there was also a significant difference between the age-standardized incidence rates in Perth and Newcastle in 1981 whereas in 1961 there was no difference in incidence in the two cities (for crude rates). This is most likely explained by differing case ascertainment. A proportion of the increase in incidence in Hobart is also likely to have resulted from improved case ascertainment there in 1981. Differential immigration of a population at a higher risk of developing MS than the indigenous population also appears to have influenced incidence rates at least in Perth and Hobart. The crude incidence rates for overseas born patients (Table 14) was higher in these two cities but, as with prevalence, age-standardization removed much of this difference and it was not significant in either city. However, the greater than expected contribution to incidence from overseas born patients in Perth and Hobart is more clearly seen in Table 15; this is likely to have contributed to the increase in incidence in Hobart and to the stability of this statistic in Perth. Therefore, in the light of these alternative explanations for the increase in incidence in Newcastle and Hobart, there was no clear evidence for a real increase in disease frequency in any city. Indeed, most studies for which serial data on incidence are available and which have reported an increase in prevalence on resurveying the same area on two or more occasions, have found that the incidence rates have generally remained stable (e.g., Percy *et al.*, 1971; Millar, 1972; Shepherd and Downie, 1980; Poskanzer *et al.*, 1980; Granieri *et al.*, 1983, 1985; Kranz *et al.*, 1983; Grønning and Mellgren, 1985), the conclusion therefore being that the observed increase in prevalence rates was related to longer survival or better case ascertainment or both.

In summary, this study has, first, confirmed the relationship between increasing prevalence of MS and increasing south latitude in Australia and, secondly, demonstrated a significant increase in prevalence in all three cities studied. The incidence of MS in Perth had remained essentially stable over the same time period but had increased in Newcastle and Hobart although this was not significant in either city. The increase in prevalence in each city (and incidence in Newcastle and Hobart) was most likely due to a combination of factors which included better case ascertainment (Newcastle and Hobart), increased recognition of the less severe forms of the disease (all cities), increased survival (all cities) and differential migration of a population at a greater risk of developing MS than the indigenous population (Perth and Hobart). Finally, analysis of MS prevalence rates amongst migrant populations in Perth and Hobart suggests that either the risk of acquisition of MS may extend over a wider age range than is generally accepted or that environmental factors prevalent in the former city have modified disease expression there.

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# KUFS' DISEASE: A CRITICAL REAPPRAISAL

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## SUMMARY

A review of 118 cases published as Kufs' disease revealed only 50 cases, including 2 patients described herein, that fulfilled our criteria for this diagnosis. Of the other 68 cases, 16 had inadequate data for analysis, 21 had evidence of a storage disease other than Kufs' disease, 10 did not have clear evidence of any neuronal storage, and 21 had atypical clinical features considered outside the spectrum of Kufs' disease. The 50 cases accepted as Kufs' disease comprised two clinical phenotypes; progressive myoclonus epilepsy (Type A) and dementia with motor disturbances (Type B). Marked photosensitivity was a striking feature of some Type A cases, and facial dyskinesias were common amongst Type B patients. Onset was typically at around the age of 30 years. A few cases began in adolescence; these differ from the protracted juvenile form of neuronal ceroid-lipofuscinosis by the absence of visual failure. Demonstration of fingerprint profiles or granular osmiophilic deposits by electron microscopy is mandatory for definitive diagnosis. Urinary sediment dolichol levels were markedly elevated in our 2 cases. This biochemical finding confirms the relationship of Kufs' disease to the early forms of neuronal ceroid-lipofuscinosis and is consistent with our hypothesis that these diseases are due to defects in the intracellular processing of lysosomal and related membranes.

## INTRODUCTION

Kufs' disease (Kufs, 1925, 1927, 1929, 1931 (fig. 1) is the late onset form of a group of lysosomal storage disorders, known as the neuronal ceroid-lipofuscinoses (NCL) or Batten-Kufs' disease. The hallmark of this group of disorders is the accumulation in neurons and other cells of abnormal lipopigments with characteristic ultrastructural patterns (Zeman, 1976; Carpenter *et al.*, 1977; Lake, 1984).

The precise nature of the storage material and the basic enzymatic defects in these disorders are not known. Subgroups have been defined on the basis of clinical, pathological, genetic and electrophysiological studies. The infantile (Haltia-Santavuori), late infantile (Jansky-Bielschowsky) and juvenile (Spielmeyer-Vogt) forms have emerged as discrete, well-defined autosomal recessive disorders. Clinical onset of these early forms, which are sometimes collectively referred to as Batten's disease, is virtually always before the age of 10 yrs (Zeman *et al.*, 1970; Lake, 1984). Recently, variant forms of early juvenile (Lake and Cavanagh, 1978) and protracted

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FIG. 1. Hugo Friedrich Kufs was born in 1871 near Leipzig in Saxony, and spent his whole life in that area. He developed an early interest in neuropathology and became one of the pioneers in this field. In addition to his meticulous descriptions of adult neuronal ceroid-lipofuscinosis, he studied familial cavernous haemangiomata, neurosyphilis, Niemann-Pick disease, cysticercosis and the dementias. He preferred the calm and security of working in the public service and was named professor by the government in 1925. After retirement, he worked until the age of 83 at the University of Leipzig He died in 1955

juvenile (Goebel *et al.*, 1976) have been proposed, but it is as yet unclear if these represent separate genetic subgroups. All these disorders are characterized by progressive cerebral and retinal degeneration, and they were previously included under the broad and outdated rubric of 'amaurotic familial idiocy'.

Kufs' disease differs from the early forms by the absence of pigmentary retinal degeneration—'amaurotic idiocy without amaurosis' (van Bogaert, 1962)—and by a later age of onset. Cases of adult onset clearly belong to this category. Cases with an earlier onset, but without visual changes, are often also regarded as examples of Kufs' disease (Libert *et al.*, 1982). Kufs' disease is rare, no characteristic clinical profile has emerged, and pathological diagnosis may be difficult and even open to question. In this report, we first describe a new family. The difficulties in the diagnosis are then briefly explored and, after a critical review of the published literature, we propose some guidelines for the clinical, biochemical and pathological diagnosis of this disorder.

## REPORT OF A FAMILY

### *Case 1 (V-22)*

This woman was well until aged 30 yrs when recurrent seizures began, and at aged 32 yrs prominent myoclonus was noted. The myoclonus was worse with her menses, markedly exacerbated by light and, at times, bouts of myoclonic status occurred. Major attacks began without an aura, and consisted of tonic-clonic seizures lasting about 1 to 2 min, often preceded by myoclonus. The family also reported seizures with tonic stiffening lasting 10 to 45 min, but these were not observed in hospital.

She was evaluated when aged 33 yrs when she could no longer walk or care for herself. Any voluntary movement was interrupted by symmetric myoclonic jerking of the limbs at about 2 Hz. Eyelid myoclonus and myoclonic dysarthria with jerking of the tongue, palate and chest were observed. Ophthalmological examination revealed visual acuity of 20/20, normal colour vision and normal fundi. There were no signs of involvement of the pyramidal, extrapyramidal, lower motor neuron or sensory systems Cerebellar testing was difficult because of the myoclonus, but there did appear to be some appendicular dysmetria and impairment of rapid alternating movements. Gait could not be assessed. There was evidence of early dementia, but formal psychological testing was not performed. General examination was normal

Routine haematological and biochemical tests, including CSF examination were normal. Serum and leucocyte hexosaminidase assays, leucocyte beta galactosidase, and urinary and plasma amino acid levels were normal. CT scan showed minimal generalized atrophy. Diagnosis was established by brain biopsy (*see* below).

Treatment with combinations of phenytoin, carbamazepine, clonazepam, barbiturates, valproic acid and 5-hydroxytryptophan with carbidopa did not result in sustained improvement. Intractable seizures and progressive dementia resulted in the need for permanent hospitalization at the age of 34. At age 43, she was severely demented and unable to communicate. She was able to see, but visual acuity could not be assessed. Myoclonus and major seizures continued She died at 44 yrs of age.

*Case 2 (V-23)*

This younger sister of Case 1 had an EEG performed at the age of 31 yrs Photic stimulation induced a tonic-clonic seizure, and skin biopsy was consistent with Kufs' disease (*see* below)

Spontaneous seizures began at age 33 and were of a number of types. Myoclonus was initially reported at night, but it remained mild. The most frequent type of attack comprised sudden loss of consciousness, sometimes preceded by a vertiginous sensation, followed by hypotonia and unconsciousness lasting up to 15 min Eyelid fluttering and occasional myoclonic jerks were sometimes observed during these attacks. Convulsive seizures occurred rarely up to the age of 36, when their frequency gradually increased to almost daily at aged 40. These seizures were sometimes preceded by myoclonus and consisted of continuous or interrupted periods of tonic stiffening with flexion of the arms and extension of the legs Attacks in hospital lasted up to 10 min, with possible longer attacks at home. Seizures were exacerbated by menstruation and by flashing lights. Visual hallucinations occurred between ages 33 and 38 yrs and were of elementary and complex types, the latter consisting of people without heads coming towards her. At times these hallucinations preceded the seizures, but it was unclear if they were true visual auras. She also had migraine, which was not directly associated with the seizures or hallucinations. She worked as a bookkeeper until aged 37 when memory difficulties began.

She was evaluated repeatedly between the ages of 33 and 40. General and neurological examinations were normal apart from mild progressive cognitive impairment apparent from the age of 38, slight impairment of rapid alternating movements at age 40, and myoclonus which was often absent, or only seen in the outstretched hands. Gait was normal, as was visual acuity, colour vision and fundoscopic examination. Psychological testing at age 40 revealed a full scale IQ of 69 with evidence of recent deterioration. She was treated with a variety of anticonvulsants. Valproate and clonazepam appeared to be of most benefit, but only a modest reduction in seizure frequency was achieved.

*Electrophysiological studies*

EEG in Case 1 (aged 33 yrs) showed generalized spike and slow wave complexes and polyspike and wave complexes at a frequency of 1–2 Hz. The background activity was abnormal and consisted mainly of 6–7 Hz rhythms. Intermittent photic stimulation at frequencies of 1–100 Hz elicited a marked photoparoxysmal response. Polygraphic study showed that multiple spike discharges were frequently synchronized with myoclonus and that the slow wave component of the EEG discharge was often associated with brief EMG silence in limb musculature (fig. 2).

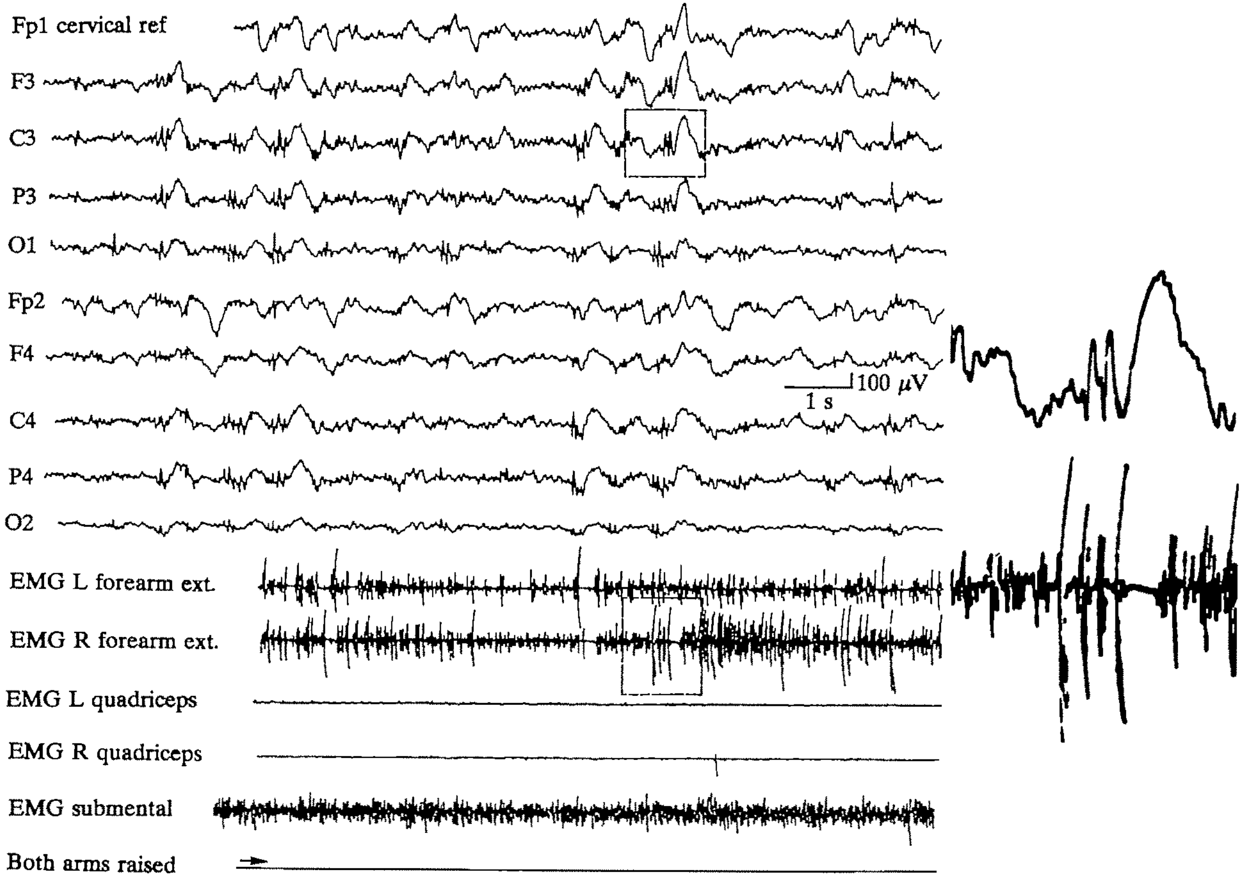

FIG. 2. *Case 1.* Polygraphic study showing generalized bilaterally synchronous polyspike-and-wave complexes and myoclonic jerks. The patient had her arms raised. The enlargement shows a segment of EEG recorded from C3 and the corresponding EMG from the right forearm extensor muscles. The EEG polyspike component was associated with myoclonic EMG responses emerging above the background tonic EMG activity During the EEG slow wave, tonic activity in the right forearm extensors temporarily vanished, while tonic activity in the EMG of the submental muscles showed no change. Reproduced from Gloor (1979) with kind permission of the author and publisher

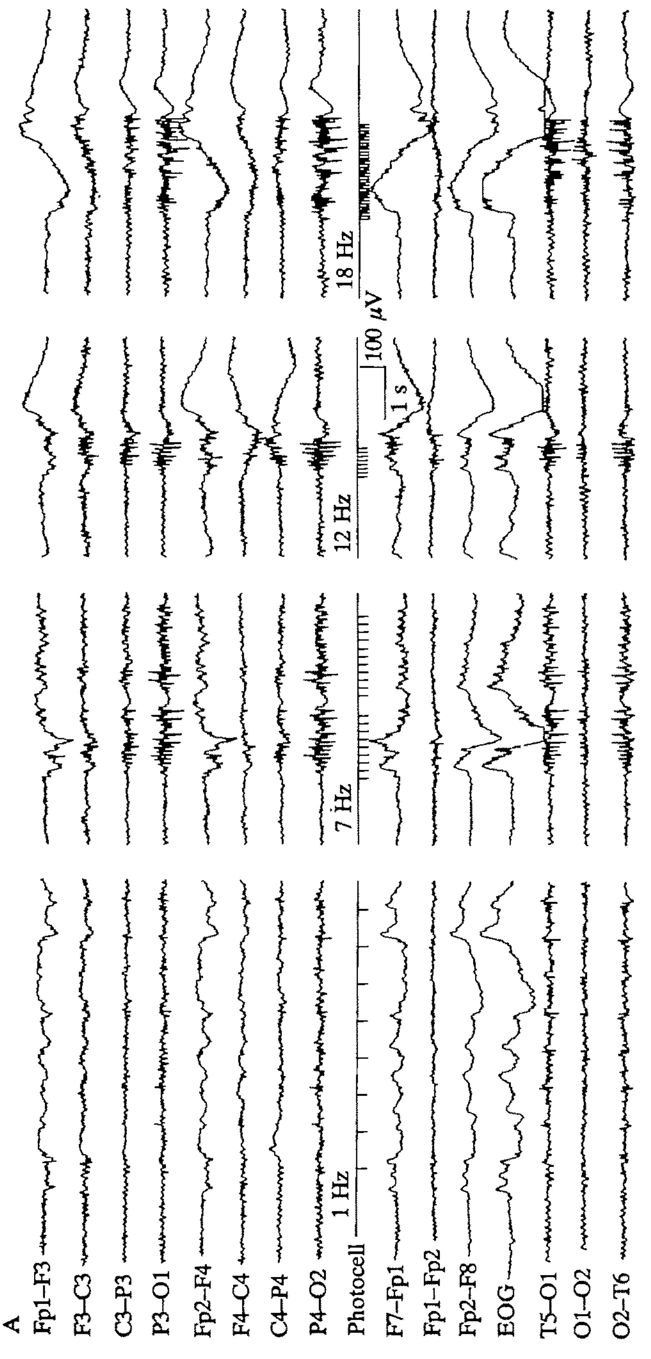

FIG 3. *Case 2.* A, EEG with intermittent photic stimulation showing a marked photoparoxysmal response at flash frequencies of 1–18 Hz

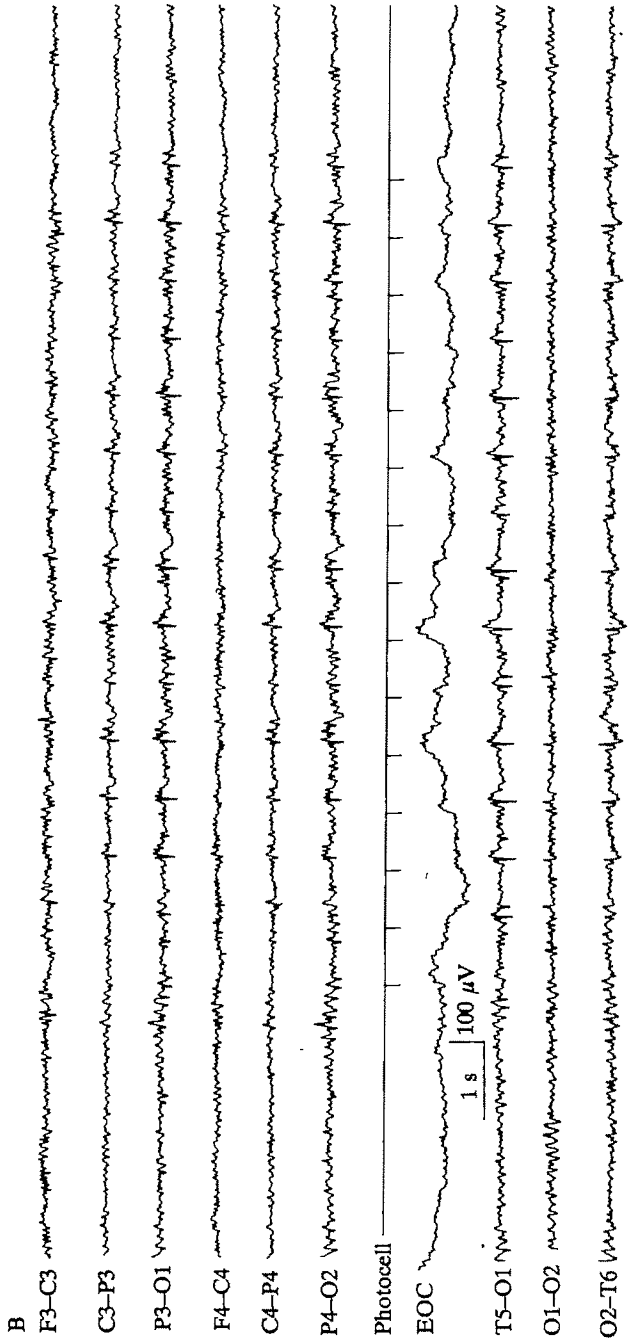

FIG. 3. *Case 2* B, a separate enlarged segment of EEG showing a clear paroxysmal response even at a flash frequency of 1 Hz.

The EEG in Case 2 was different in that, even at age 40, the background activity was normal, and spontaneous epileptiform discharges were very rare. Intermittent photic stimulation did, however, provoke a marked photoparoxysmal response even at flash frequencies of 1 Hz (fig. 3). The visual evoked responses were of normal latency and amplitude in both eyes. Nerve conduction velocities were normal, and somatosensory evoked potentials did not show giant potentials. Flash electroretinograms revealed b waves of normal amplitude, latency and wave form. Pattern electroretinograms, performed according to the method of Kirkham and Coupland (1983), were also normal.

### *Pathology*

*Case 1.* In a biopsy of the right frontal lobe, paraffin sections stained with Sudan black showed that about 25% of the large neurons of the third and fifth cortical layers had an excess of brown staining material which filled much of their cytoplasm and often distended the proximal axon. The nuclei of these cells tended to be displaced to one side or towards the apical dendrite. Minor amounts of similar staining material were visible in most cells of the sixth cortical layer and in a few cells of the second and fourth layers. In cresyl violet preparations, the distended axons stained pale blue, while the stuffed cell bodies tended to appear darker because they were studded with blue-violet dots against a pale blue background. In occasional cells with distended axons, the perikaryon appeared shrivelled. There was no evidence of storage in the meninges. Semithin epoxy resin sections displayed the storage particularly well (fig. 4). By electron microscopy, irregularly shaped membrane-bound cytosomes averaging about 1 μm in diameter were found in neuronal cell bodies and proximal axonal segments. They were packed with fingerprint profiles and many also contained a lipid vacuole (fig. 5). Ordinary lipofuscin granules were not seen in neurons, but they were present in astrocytes in small numbers

Skeletal muscle biopsy showed a few acid phosphatase positive sites in muscle fibres and in interstitial cells. Electron microscopy showed no storage. A sural nerve biopsy showed a small amount of Wallerian degeneration. A skin biopsy by phase microscopy on semithin sections showed what appeared to be normal amounts of lipofuscin in eccrine secretory cells. Electron microscopy on these cells disclosed scattered cytosomes with fingerprint profiles that were sometimes associated with lipid droplets. These cells also contained typical lipofuscin bodies which were considerably more numerous than the cytosomes with fingerprint profiles Myoepithelial cells and duct cells were negative. In melanosome-containing cells of a hair bulb, a few cytosomes with rectilinear and fingerprint profiles were found. A liver biopsy by light and phase microscopy showed a fatty liver. By electron microscopy, occasional hepatocytes contained small cytosomes with rectilinear and fingerprint profiles. Rather more numerous, however, were small lamellar bodies in the hepatic cells. These were considered nonspecific In a rectal biopsy, dense granules were seen within neurons of Meissner's plexus, although the cells did not appear distended. These cells could not be visualized by electron microscopy.

*Case 2.* Sections of skin were examined by electron microscopy. Fingerprint profiles were found in the eccrine secretory cells. Typical lipofuscin bodies were also seen (fig. 6).

### *Genetics and urinary dolichol studies*

The 2 affected sisters were from a sibship of 5. Ancestors of both parents came from adjacent small villages in Frosinone, an Italian province southeast of Rome. Although a number of consanguineous marriages did occur in the pedigree, there was no known parental consanguinity (fig. 7). The parents, 3 younger siblings and offspring of the patients were clinically unaffected The 3 siblings had EEGs with photic stimulation and skin biopsies examined by electron microscopy; all were normal. A maternal aunt (IV-3) had had seizures from the age of 17 yrs, which were attributed to a fall from a tree. She died at the age of 58 yrs and may have been demented No further clinical details and no pathological data are available.

Urinary sediment dolichol levels were estimated on 24 h urine specimens according to the method of Wolfe *et al.* (1986*a*). Three generations of the family were studied, and results are shown in Table

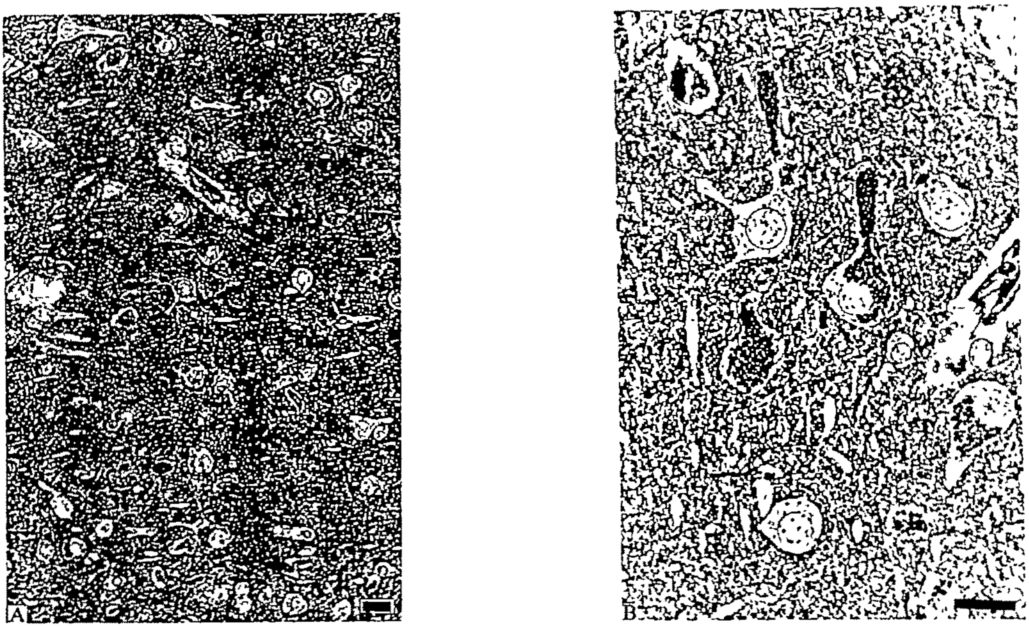

Fig. 4. *Case 1,* brain biopsy. A, resin section, in which some of the large neurons of the third cortical layer show accumulations of dark staining material in their cell body and/or proximal axon, while others appear spared. B, at higher magnification the storage appears in the form of distinct granules. Paraphenylene diamine, phase optics. Bars = 20 $\mu$m.

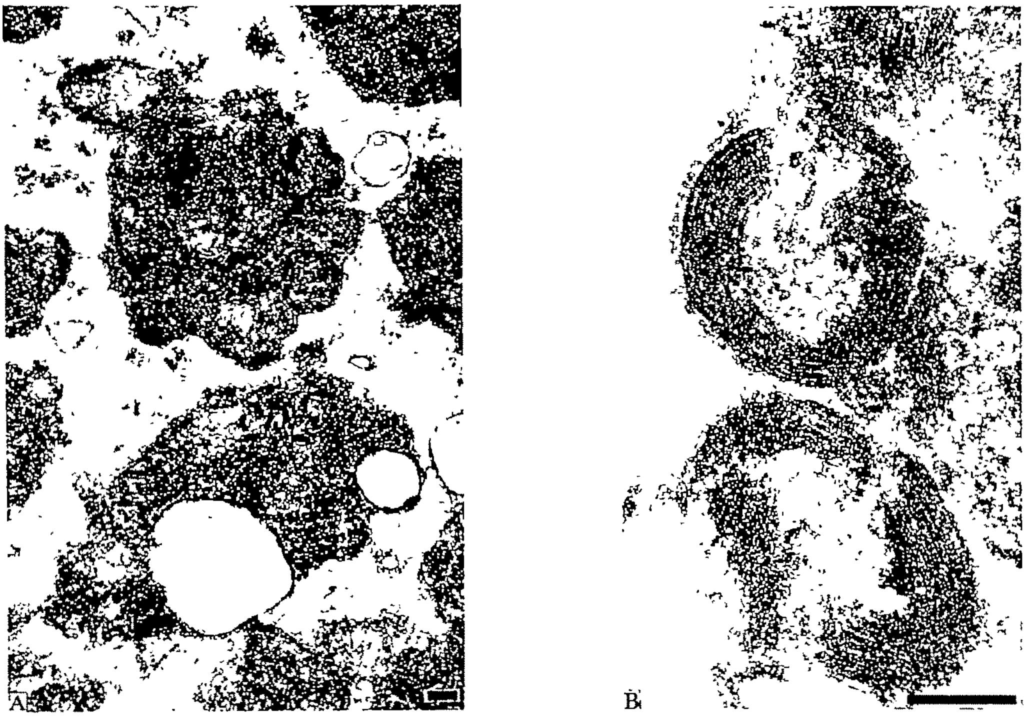

Fig. 5. *Case 1,* brain biopsy. A, electron micrograph from an axon showing storage cytosomes which contain numerous fingerprint profiles as well as poorly defined lamellar fragments. In the cytosome to the right, there are two lipid droplets. B, electron micrograph showing the distinctive paired parallel line structures of fingerprint profiles. Bars = 0.1 $\mu$m.

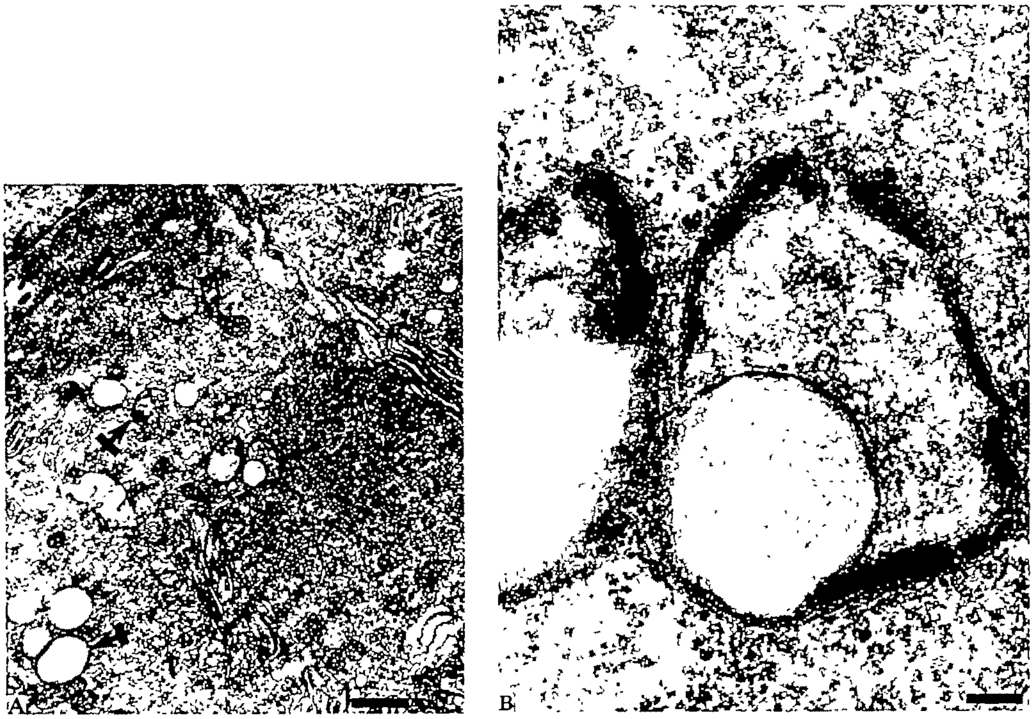

FIG. 6. *Case 2*, skin biopsy. A, electron micrograph showing parts of eccrine secretory cells containing fingerprint profiles (single arrow) as well as lipofuscin (barred arrows) At this power they cannot reliably be distinguished. Bar = 1 µm. B, at higher magnification the fingerprint profiles in the eccrine secretory cell can be recognized. Bar = 0.1 µm

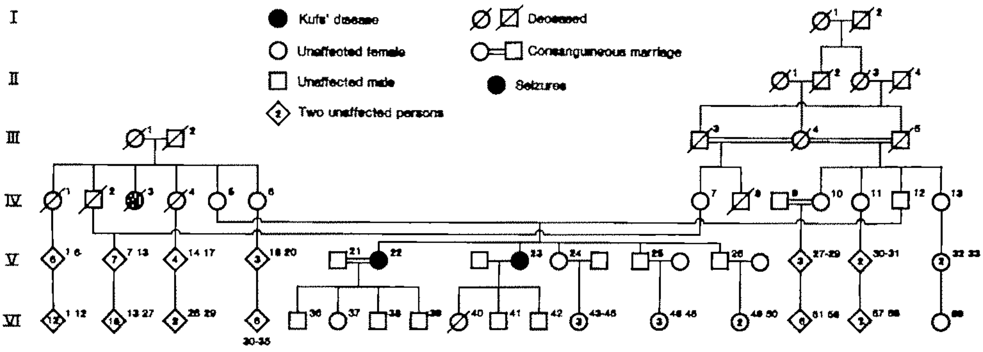

FIG. 7. Family pedigree.

1. Values for the 2 patients were markedly elevated. With the exception of 1 sibling (V-24), the levels of the parents, siblings and offspring were within the normal range. The dolichol values for V-24 were elevated, but at the age of 38 yrs she appears to be unaffected on the basis of clinical, EEG and skin biopsy data, so this single estimation may represent a false positive result.

TABLE 1 URINARY SEDIMENT DOLICHOL LEVELS IN THREE GENERATIONS OF A KUFS' DISEASE FAMILY

| | | *Dolichols* | | |
|---|---|---|---|---|
| *Subjects* | *Age (yrs)* | *μg/mg lipid* | *μg/dl* | *μg/g creatinine* |
| Parents | | | | |
| IV-5, Mother | 64 | 1.4 | 2.3 | 13.0 |
| IV-12, Father | 62 | 2.7 | 2.3 | 13.0 |
| Patients | | | | |
| V-22, Case 1 | 43 | 4.2* | 31.1 | 111.9 |
| V-23, Case 2 | 40 | 15.3 | 30.7 | 295.2 |
| Siblings | | | | |
| V-24, sister | 38 | 6.3 | 5.3 | 41.2 |
| V-25, brother | 36 | 4.3 | 2.8 | 18.5 |
| V-26, brother | 28 | 2.2 | 2.5 | 9.3 |
| Offspring | | | | |
| VI-36, son of Case 1 | 21 | 2.4 | 3.1 | 15.1 |
| VI-37, daughter of Case 1 | 20 | 4.0 | 2.4 | 23.1 |
| VI-38, son of Case 1 | 17 | 1.6 | 0.9 | 5.8 |
| VI-41, son of Case 2 | 14 | 0.9 | 0.9 | 8.7 |
| VI-42, son of Case 2 | 10 | 3.1 | 1.0 | 14.6 |
| Controls† | | | | |
| Normals (n=30) | 30–57 | 1.9±1.6<br>(0–3.5) | 1.6±1.0<br>(0–3.2) | 14.2±9.0)<br>(0–41.0) |

*Level on a lipid weight basis is relatively low due to large excess of urinary sediment lipid as a consequence of an indwelling urinary catheter. †Control subjects expressed as means ±SD with range in brackets

## REVIEW OF PUBLISHED CASES

### *Clinical problems*

There are considerable difficulties in deciding which cases should be accepted. In the early literature, Kufs' disease was sometimes loosely equated with all types of adult lipidosis. As discussed below, it is likely that a number of cases published as Kufs' disease actually represent other specific and recently recognized storage diseases of adulthood such as sialidosis type II, Niemann-Pick disease group II and late-onset forms of the gangliosidoses. Inclusion of these cases has confounded the clinical delineation of Kufs' disease.

The clinical features of cases described in the literature as Kufs' disease are very heterogeneous. The age of onset varies from 11 to 50 yrs in definite cases (Greenwood and Nelson, 1978; Goebel *et al.*, 1982) and from 3 to 64 yrs in cases where we doubt the diagnosis (Hallervorden, 1938*a*; Vallat *et al.*, 1985). Reported presenting features include behaviour change, seizures, ataxia, abnormal movements, spasticity, psychosis, amyotrophy and dementia. The clinical course, from onset to death, has been reported to be as short as 1 yr or as long as 54 yrs (Hallervorden, 1938*a*; Bignami *et al.*, 1969). The rarity and diversity of cases reported as Kufs' disease has precluded clinical recognition of the disorder, and antemortem diagnosis has rarely been possible.

### *Pathological problems*

The diagnosis depends on the demonstration of accumulation of certain abnormal lipopigment deposits. Lipopigment is here defined as any autofluorescent substance which stains with lipid stains, but is insoluble in lipid solvents.

Difficulties in pathological diagnosis are principally of two types. First, lipofuscin, and lipopigment which accumulates in neurons and other cells in normal ageing, may be misinterpreted as abnormal storage. The amount seen in normal anterior horn cells, for example, especially by electron microscopy, may be startling. The stored material in Kufs' disease, and in other forms of NCL, is virtually colourless on unstained slides and gives a pale yellow fluorescence. In contrast, lipofuscin is yellowish-brown on unstained slides and gives orange fluorescence (Carpenter *et al.*, 1977).

The second difficulty is that the storage material of Kufs' disease may be difficult to distinguish from that of other storage diseases by light microscopy. In those diseases, the stored material, although not primarily autofluorescent, may eventually acquire that property as it persists in lysosomes. Particularly in late onset forms, autofluorescent deposits tend to be widespread in the brain. Staining with Sudan stains and PAS is positive in most storage diseases and does not help to distinguish between them. In NCL, granules may fill the cell bodies, round their contours, and displace the nucleus towards the apical pole, but the cell bodies do not become enlarged as they do in Tay-Sachs disease. In the pyramidal cells of the cortex, storage in NCL frequently extends into the proximal axon, but this phenomenon may also be seen in late onset gangliosidoses (Goldman *et al.*, 1981). In general, it is difficult to evaluate the numerous reports of Kufs' disease in which ultrastructural studies are not available.

As regards the diagnostic ultrastructural characteristics of their storage, cases of Kufs' disease fall into two groups. In the first, the storage in neurons contains abundant fingerprint profiles, usually mixed with a variable proportion of crescentic or straight lamellar profiles (rectilinear profiles), which may form stacks or simply appear as two lines enclosing a lucent space. The fingerprint profiles themselves should conform exactly to published descriptions (Carpenter *et al.*, 1977). They are formed of systems of paired parallel lines, either straight or curving. Each line of about 2.3 nm is separated from its neighbour by a lucent space of 1.5 nm and from the adjacent pair by a space of 2.5 nm. Magnification of × 100,000 on prints is needed for proper identification. Various other formations may have some resemblance to human fingerprints, but not to fingerprint profiles and they have no diagnostic significance in Kufs' disease.

In the second ultrastructural type, the storage is characterized by granular osmiophilic deposits (GRODs). This pattern is seen in the infantile form of NCL, and in occasional juvenile cases, which are clinically indistinguishable from juvenile cases with fingerprint profiles. GRODs may be difficult to distinguish from lipofuscin on electron microscopy, but their granularity is more uniform, they are less likely to have lipid vacuoles incorporated into them, and the individual aggregates are considerably larger (Carpenter *et al.*, 1973).

### *Criteria used in assessing published cases*

We reviewed all available reports where the original authors or subsequent reviewers had regarded the case as Kufs' disease, adult amaurotic idiocy or diffuse lipofuscinosis. Our evaluation was made largely on the basis of the pathological data. Clinical information influenced the assessment only when very atypical features were present, such as cherry-red spots or organomegaly. The cases were divided into two major groups; one where we considered the diagnosis of Kufs' disease unlikely, and the other where it was possible or definite. A third and final group comprised cases fulfilling the criteria for NCL in which there were rather unusual features; included here are cases of childhood onset without visual failure, and examples of the protracted juvenile subgroup.

Ultrastructural demonstration of fingerprint profiles or GRODs in the presence of otherwise typical light microscopic findings was considered the most definitive evidence of Kufs' disease. Few reports met this criterion and some studies with ultrastructural data showed micrographs that were unclear or at too low magnification for conclusive diagnosis. In the majority of reports, the judgement was based on less definitive light microscopic descriptions.

The reports of Winkelmann (1947), Perris and Strandqvist (1969), Kamijyo *et al.* (1969), Clayton and Schiffman (1986), Case 19 of Zeman and Dyken (1969), Cases D and G of Edgar and Post (1963) and the 'R' and 'Bark' families of van Bogaert (1962) were excluded from the analysis because the published pathological data were inadequate to make even a superficial evaluation.

### *Cases unlikely to be Kufs' disease*

Table 2 lists 31 cases in 24 reports where we considered the diagnosis of Kufs' disease to be unlikely. In 21 of these cases a storage disorder other than Kufs' disease was present, whereas in 5 cases we were not convinced that any abnormal storage was demonstrated. In the remaining 5 cases the presence of storage material was equivocal (Table 2).

The 21 cases of other storage disorders illustrate well the problems in defining and diagnosing Kufs' disease. In some of these cases, with the help of hindsight and of recent advances in classification of storage disorders, alternative diagnoses can be suggested. Kitagawa *et al.* (1962) and Tokuda *et al.* (1967) described a Japanese patient with myoclonus epilepsy, ataxia, cherry-red spots and angiokeratomas who had 2 affected siblings. The histological and histochemical findings were compatible with Kufs' disease. The clinical features are, however, very suggestive of sialidosis type II, which is a recently defined disorder found predominantly in Japan (Lowden and O'Brien, 1979; Matsuo *et al.*, 1983; Warner and O'Brien, 1983). The light microscopic features of sialidosis and Kufs' disease may be roughly

TABLE 2 PUBLISHED CASES NOT FULFILLING THE CRITERIA FOR KUFS' DISEASE

| *Authors* | *Onset* (*yrs*) | *Death* (*yrs*) | *Clinical features* | *Comments* |
|---|---|---|---|---|
| Cases of other storage diseases | | | | |
| Meyer (1931) | 18 | 26 | Dementia, rigidity, dysarthria | Storage disorder, type unknown Enlarged spleen; light microscopy not suggestive of NCL |
| Hallervorden (1938*a*), Case 2 | 3 | 57 | Three affected brothers; ataxia, dysarthria, amyotrophy | Pathology not typical of NCL Clinically suggestive of late form of $G_{M2}$ gangliosidosis |
| Marques (1947) | 9 | 17 | Affected sibling, dystonia, dysarthria, dementia | Cells very swollen for NCL Possibly late-onset gangliosidosis |
| Moschel (1954) | 15 | 39 | Tremor, dysarthria, paraparesis, psychosis, involuntary movements | Storage disorder, type unknown Light microscopy not suggestive of NCL Excessive pigment |
| Simma (1957, Seitelberger and Simma (1962) | 14 | 33 | Affected sibling, behaviour change, dyskinesias, dementia | Storage disorder, type unknown Cells quite swollen. Excessive pigment |
| Zeman and Scarpelli (1958) | 5 | 20 | Unsteadiness, rigidity, dementia, hepatosplenomegaly | Storage disorder, type unknown Clinical and pathological features very atypical for NCL Excessive pigment |
| Fine *et al* (1960) | 37 | 54 | Amyotrophy, ataxia, dysarthria | Pathology not typical of NCL Clinically suggestive of late form of $G_{M2}$ gangliosidosis |
| Zeman and Hoffman (1962) | 18 | 53 | Unusual biphasic illness; severe subacute ataxia and spasticity which resolved, later onset of dementia, seizures, optic atrophy and retinitis pigmentosa. Two cousins had typical juvenile NCL | Probably storage disease, brain poorly fixed Light microscopic findings equivocal. Very atypical clinical features |
| Edgar and Post (1963), Case A2 | 4 | 51 | Seizures, personality change, dementia. | Storage disorder, incomplete description, not suggestive of NCL |
| Kitagawa *et al* (1962), Case 2; Tokuda *et al* (1967) | 21<br>19<br>16 | 36<br>23<br>25 | Three affected sibs, ataxia, myoclonus, seizures, dysarthria, cherry-red spots, corneal clouding, angiokeratomas | Storage disorder Clinical picture highly suggestive of sialidosis type II |
| Escolá Picó (1964) Case 1 | 26 | 31 | Behaviour change, dementia | Storage disorder, type uncertain Ultrastructure not suggestive of NCL |
| Escolá Picó (1964), Case 2 | ? | 51 | Depression | Storage disorder, type uncertain Ultrastructure not suggestive of NCL. |
| Bignami *et al.* (1969) | 35 | 35 | Myoclonus, ataxia, mutism, dyskinesias, apathy, impaired upgaze. Acute course | Storage disorder, type uncertain Not NCL as lipid was extractable, cells very swollen and spleen involved |
| De Vries (1968) | 27 | 42 | Early retardation then dementia, ataxia, chorea | Storage disorder, type uncertain Cells too swollen for NCL. |
| Chou and Thompson (1970) | 17 | 32 | Seizures, dysarthria, dementia, dyskinesias | Ultrastructure suggestive of Niemann-Pick disease group II |
| Hamaguchi *et al* (1971) | 23 | 31 | Seizures, myoclonus, ataxia, dysarthria, amyotrophy | Storage disorder, type unknown Ultrastructure not suggestive of NCL |
| Spalke *et al* (1972) | 39 | 53 | Ataxia, dyskinesias, dementia, splenomegaly | Large vacuolated cells in spleen and ultrastructural features suggest Niemann-Pick disease group II |

| *Authors* | *Onset (yrs)* | *Death (yrs)* | *Clinical features* | *Comment* |
|---|---|---|---|---|
| Kornfeld (1972) | 15 | 26 | Dyskinesias, ataxia, dementia. | Swollen cells in liver and spleen and ultrastructural features not suggestive of NCL, possibly Niemann-Pick group II. |
| Horoupian and Ross (1977) | 20 | 25 | Myoclonus seizures, ataxia, renal failure | Clinical and pathological features of action myoclonus-renal failure syndrome. |
| Cases with no definite evidence of storage material | | | | |
| Pilotti (1921) | 33 | 38 | Myoclonus, dysarthria, rigidity, depression | No storage demonstrated in neurons |
| Roizin *et al.* (1962) | 22 | 34* | Retinitis pigmentosa, dementia, ataxia | Rectal biopsy with no evidence of storage |
| Feldman *et al* (1969) | 20 | 80 | Tremor, ataxia, dysarthria | Normal lipofuscin shown. |
| Badurska *et al* (1981) | 32 | 40* | Seizures | Normal tubular arrays in lymphocytes shown |
| Sandyk (1981, 1982) | 29 | —* | Psychosis, myoclonus, rigidity | Normal lipofuscin shown |
| Cases with equivocal evidence of storage | | | | |
| Wagner (1949) | ? | ? | Visual loss, dementia | Sketchy description, cells swollen but storage not clearly shown |
| Jervis and Pullarkat (1978) | 3 | 36 | Mental retardation spasticity, optic atrophy, dyskinesias | Severe brain atrophy, neurofibrillary tangles, possible storage material in neurons, not suggestive of NCL |
| Galatioto *et al* (1985) | 40 | 49 | Parkinsonism, spasticity, amyotrophy, dysarthria. | Storage not clearly demonstrated |
| Vallat *et al* (1985) | 64 | 68 | Dementia, tremor, myoclonus | Nerve biopsy showing either normal pi granules or possibly evidence of metachromatic leucodystrophy |
| Dawson *et al* (1985) Case 2 | ? | 20* | Perinatal trauma, seizures, mental retardation gait deterioration at age 19 yrs | Inadequate pathological description and illustration |

*Indicates patient still alive at time of report

similar, but these disorders are now easily distinguished by clinical, biochemical and ultrastructural criteria (Lake, 1984; Berkovic *et al.*, 1986). Similarly, Jellinger *et al.* (1982) have emphasized that the histological features of late forms of $G_{M2}$ gangliosidosis can be confused with those of Kufs' disease. The patients of Hallervorden (1938*a*) and of Fine *et al.* (1960) were originally regarded as having Kufs' disease, but the descriptions would be more consistent with recently described forms of $G_{M2}$ gangliosidosis with phenotypes mimicking spinocerebellar degeneration and spinal muscular atrophy (Johnson, 1981). Unfortunately, the lack of biochemical or ultrastructural data makes it impossible to confirm this speculation in these cases.

Another disorder, which has also been confused with Kufs' disease, is Niemann-Pick disease group II, also known as Niemann-Pick type C or juvenile dystonic lipidosis. In addition to the specific storage material, whose nature has not been clarified, there may be abundant accumulation of lipopigment in viscera, although not in neurons. The ultrastructural appearance of the storage material is distinctive; neurons contain membrane-bound polymorphous cytoplasmic bodies containing loosely-packed lamellae which often appear concentric. The diagnosis may also be suggested by the finding of large foamy macrophages in the bone marrow, lymph nodes and spleen (Elfenbein, 1968; Karpati *et al.*, 1977; Pellissier *et al.*, 1976; Lake, 1984). The case of Chou and Thompson (1970), published as Kufs' disease, is now generally regarded as an example of Niemann-Pick group II (Greenwood and Nelson, 1978; Lake, 1984). The patients of Kornfeld (1972) and of Spalke *et al.* (1972) may also represent examples of this disorder.

The case of Horoupian and Ross (1977), described as an example of the 'pigment variant' of Kufs' disease, has clinical and pathological features identical to those of the recently described action myoclonus-renal failure syndrome (Andermann *et al.*, 1986). A further 12 cases (Table 2) had evidence of storage disorders that were unlikely to be Kufs' disease, but alternate diagnoses could not be formulated with the available data.

### *Cases of possible or definite Kufs' disease*

Cases that fulfill our criteria for Kufs' disease are listed in Tables 3 and 4. Only a few of these reports contain adequate electron microscopic data for a conclusive diagnosis of Kufs' disease and, in the majority of cases, we relied on light microscopic descriptions which are subject to the uncertainties described above. The cases were divided into two types on the basis of the prominent clinical features.

*Type A: seizures, myoclonus, neuropsychiatric change.* There were 29 cases, including 6 sporadic cases and 23 cases from 7 families where the clinical course was dominated by seizures, myoclonus and neuropsychiatric abnormalities (Table 3). In most of these cases, as in the family reported here, the initial symptom was a seizure, and the course was typical of the syndrome of progressive myoclonus epilepsy with intractable seizures, myoclonus and dementia (Berkovic *et al.*, 1986). In 3 cases (Ishino *et al.*, 1972; Tobo *et al.*, 1984), behaviour change was the initial symptom, and seizures were less prominent. The only other common neurological signs were ataxia and dysarthria, but these were usually not the presenting features nor were they severe except in the terminal stages. Similarly, signs of involvement of the pyramidal, extrapyramidal and lower motor neuron systems were generally absent or only seen terminally. Optic atrophy or pigmentary retinopathy were not present in any patient. Visual impairment was noted only in the case of Aihara *et al.* (1976), where it was associated with an unspecified type of macular degeneration.

The nature of the seizures was of some interest. Some of the major convulsions in the present family were remarkably long, with periods of continuous or interrupted generalized tonic stiffening lasting 10 to 40 min. Other attacks consisted of a sudden collapse with hypotonia and stupor lasting for up to 15 min, sometimes associated with eyelid fluttering. These attacks were never recorded on EEG, so their epileptic nature was only suspected and not confirmed. Similar attacks were noted by Boehme *et al.* (1971) and Tobo *et al.* (1984); the latter authors documented

TABLE 3 DEFINITE OR POSSIBLE CASES OF KUFS' DISEASE WITH TYPE A CLINICAL PHENOTYPE (PROGRESSIVE MYOCLONUS EPILEPSY)

| *Authors* | *Onset (yrs)* | *Death* (yrs)* | *Clinical features* | *Ultrastructure* |
|---|---|---|---|---|
| van Bogaert and Borremans (1937), van Bogaert (1952, 1962) | 15<br>35<br>38<br>41 | 62<br>60<br>49†<br>49† | Four affected sibs (family 'Ae'), seizures, myoclonus, dementia, hyperkinesia, ataxia, dysarthria, hallucinations | Light microscopy only |
| Greenfield (1951) | 13 | 28 | Seizures, myoclonus, ataxia, mild dementia | Light microscopy only. |
| Fattovich (1954), Allegranza (1956) | 30<br>26 | 37<br>35 | Two affected sibs, seizures, dementia, ataxia, dysarthria, myoclonus, hallucinations | Light microscopy only |
| Pallis *et al* (1967) | 49 | 55 | Myoclonus, ataxia, seizures, dementia, dysarthria | Light microscopy suggestive of Kufs, ultrastructural illustrations not diagnostic |
| Boehme *et al.* (1971), Leonberg *et al* (1982) | 40<br>32<br>30<br>32<br>31 | 48<br>42<br>44†<br>39†<br>39†<br>31†<br>32† | Autosomal dominant pattern, 7 affected in 2 generations with other probably affected members in earlier generations, seizures, myoclonus, ataxia, dementia, dysarthria | Light microscopy suggestive of Kufs in 2 cases. Ultrastructure in 1 case not well preserved but probably GRODs Findings in brain biopsy of an additional presymptomatic relative were not diagnostic (Brodner *et al.*, 1976) |
| Ishino *et al* (1972) | 27 | 42 | Behaviour change, seizures, facial dyskinesia, myoclonus, ataxia, dementia, rigidity | Light microscopy only. |
| Dekaban and Herman (1974) (Cases 11–13) | 14<br>13<br>14 | 22<br>19†<br>17† | Three affected sibs; myoclonus, seizures, ataxia, mild dementia, mild weakness | Probably GRODs |
| Aihara *et al* (1976) | 14 | 27 | Dysarthria, seizures, myoclonus, dementia, ataxia, macular degeneration | Fingerprint profiles |
| Greenwood and Nelson (1978) | 11 | 19 | Dementia, seizures, myoclonus, ataxia. | Fingerprint profiles |
| Dom *et al* (1979) Vercruyssen *et al.* (1982) | 30<br>32<br>33 | 33<br>36*<br>34* | Three affected sibs, seizures, dementia, dysarthria, myoclonus, rigidity | Fingerprint profiles |
| Goebel *et al.* (1982) (Case 1) | 50 | 56 | Seizures, behaviour change, dysarthria, mild right hemiparesis, dementia | Fingerprint profiles |
| Tobo *et al* (1984) | 30<br>36 | 49†<br>51 | Two affected sibs, psychosis, seizures, nonconvulsive status, dysarthria, ichthyosis | Light microscopy suggestive of Kufs. Ultrastructural illustrations not diagnostic. |
| This report | 30<br>33 | 43*<br>40* | Two affected sibs; seizures, myoclonus, dementia, ataxia. | Fingerprint profiles |

* Indicates patient still alive at time of report. † No pathological data, diagnosis based on affected family member.

irregular generalized spike-and-wave complexes during one attack of stupor. Case 2 described simple and complex visual hallucinations which appeared, at times, to precede seizures. Visual auras were also reported by Fattovich (1954), Boehme *et al.* (1971) and Greenwood and Nelson (1978), and visual hallucinations were noted by van Bogaert (1952, 1962). Marked photosensitivity was observed in both our patients and in the cases of Pallis *et al.* (1967), Aihara *et al.* (1976) and Vercruyssen *et al.* (1982). Myoclonus was of variable severity, from mild to disabling.

A striking feature of these 29 cases was the nonrandom nature of the ages of onset. The mean age of onset was 29.0 ± 10.5 yrs with the majority of cases clustering around the age of 30 yrs. An apparently distinct group had onset in early adolescence (fig. 8). Affected siblings had very similar ages of onset with one exception. In the family 'Ae' (Table 3), 3 siblings had their first symptoms between the ages of 35 and 41 yrs, whereas the proband had his first symptoms at age 15 yrs with worsening of the disease at age 35 yrs (van Bogaert and Borremans, 1937; van Bogaert, 1952, 1962).

Of the 29 cases, 21 had died by the time of publication; the course of the disease from onset to death had a mean of 12.4 ± 9.4 yrs and a median of 9 yrs (range 3–47). Death was usually related to progressive dementia rather than to a complication of seizures. There was no sex bias in this group; 16 males and 13 females were affected. Autosomal recessive inheritance was likely for all these cases, with the exception of 1 family (Boehme *et al.*, 1971; Leonberg *et al.*, 1982), where autosomal dominant transmission occurred.

*Type B: dementia and motor abnormalities.* Table 4 lists 21 cases where the presentation was not dominated by seizures, but rather by dementia with motor disturbances in most cases. There were 10 sporadic cases, 2 families had 2 affected siblings, and the family of Ferrer *et al.* (1980) had 6 affected individuals though only 1 was described in detail.

The initial symptoms were of behaviour change, which varied from disinterest in the usual activities of life to an overt psychosis. The organic nature of these neuropsychiatric symptoms became obvious when dementia and motor disturbances developed. Cerebellar or extrapyramidal features were prominent (Seitelberger and Nagy, 1958). Although parkinsonism was present in 1 case (Hallervorden, 1938*b*), hyperkinetic movement disorders were more common. A remarkable feature, which may be of diagnostic value, was the presence of tic-like

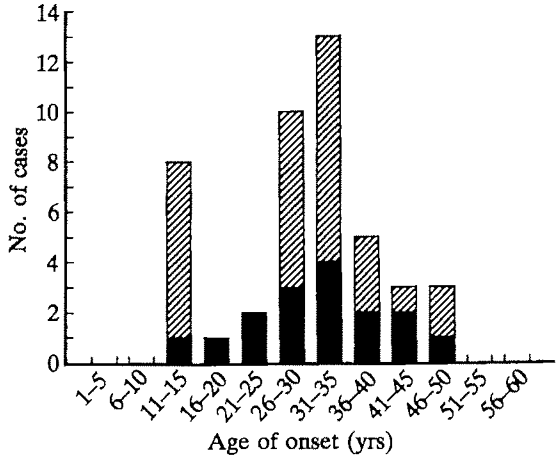

FIG. 8. Interval histogram showing ages of onset of 45 definite or possible cases of Kufs' disease Progressive myoclonus epilepsy (Type A) (hatched areas), dementia and motor disturbances (Type B) (filled areas). Precise ages of onset were not published for 5 of the Type B cases (Table 4)

TABLE 4 DEFINITE OR POSSIBLE CASES OF KUFS' DISEASE WITH TYPE B CLINICAL PHENOTYPE (DEMENTIA AND MOTOR DISTURBANCES)

| *Authors* | *Onset (yrs)* | *Death* (yrs)* | *Clinical features* | *Ultrastructure* |
|---|---|---|---|---|
| Sträussler (1906) | ? | 36 | Psychosis, dementia, ataxia | Light microscopy only |
| Kufs (1925, 1929) | 26<br>16 | 38<br>41 | Two affected sibs, psychosis, dementia, ataxia, tremor | Light microscopy only. |
| Kufs (1931) | 42 | 59 | Psychosis, dementia, rigidity, tremor, dysarthria | Light microscopy only. |
| Hallervorden (1938*a*), Case 1, Hallervorden (1938*b*) | 33 | 54 | Behaviour change, myoclonus, dysarthria, dementia, rigidity | Light microscopy only |
| Friedrich (1938) | 47 | 54 | Dementia, dysarthria. | Light microscopy only |
| Seitelberger and Nagy (1958) | 24 | 36 | Behaviour change, ataxia, facial dyskinesia, dementia, dysarthria | Light microscopy only |
| Derwort and Noetzel (1959) | 11 | 32 | Psychosis, dysarthria, ataxia, chorea, tremor, dystonia | Light microscopy only |
| Kraft (1972) | 27<br>26 | 32*<br>35† | Two affected sibs, behaviour change, dementia, ataxia, facial dyskinesia, dysarthria | Light microscopy only<br>Light microscopy only |
| Coggi (1972) | 42 | 50 | Behaviour change, dementia, seizures (late) | |
| Jakob and Kolkmann (1973) | 31 | 40 | Psychosis, dementia, spasticity, ataxia | Light microscopy suggestive of Kufs although excess of extraneuronal pigment is atypical, Ultrastructural illustrations not diagnostic |
| Tomonaga *et al* (1978) | 24 | 35 | Behaviour change, dementia, abulia, facial dyskinesia, athetosis, ataxia | Light microscopy suggestive of Kufs Ultrastructural illustrations not diagnostic |
| Ferrer *et al* (1980) | 38<br>?<br>?<br>?<br>?<br>33 | 45*<br>50†<br>50†<br>48†<br>43†<br>48† | Autosomal dominant pattern, 6 affected in 2 generations, dementia, and facial dyskinesias in all, late seizures in 1 case Onset 33–38 yrs, but details not given for 4 cases | Light microscopy suggestive of Kufs. Ultrastructural features also consistent but exact pattern is not clear |
| Goebel *et al* (1982) (Case 2), Dowson (1983) | 34 | 41 | Dementia, apraxia. | Light microscopy suggestive of Kufs. Ultrastructure not shown |
| Dawson *et al* (1985), (Case 1) | 40 | 45* | Dementia, dysarthria, ataxia, myoclonus | Light microscopy not shown or adequately described Ultrastructural illustrations not diagnostic |

* Indicates patient still alive at time of report † No pathological data, diagnosis based on affected family member

facial dyskinesias in a number of cases (Seitelberger and Nagy, 1958; Kraft, 1972; Tomonaga *et al.*, 1978; Ferrer *et al.*, 1980). One patient showed considerable spasticity and a diagnosis of multiple sclerosis was considered during life (Jakob and Kolkmann, 1973), but pryamidal signs were not prominent in other cases. Visual failure and retinal abnormalities were not present, although the case of Seitelberger and Nagy (1958) was considered to have optic nerve pallor and the unaffected father of the original sibling pair of Kufs (1925, 1929) had retinal pigmentation. Seizures did not occur with the exception of two cases who had convulsions late in the course of the disease (Coggi, 1972; Ferrer *et al.*, 1980).

The age of onset varied from 11 to 47 yrs (mean 30.9 ± 9.8 yrs, median 32 yrs). The course from onset to death was from 7 to 25 yrs (mean 12.6 ± 5.5 yrs, median 11 yrs). Seven males and 14 females were affected. Autosomal dominant inheritance was probable in the family of Ferrer *et al.* (1980), whereas in the remainder of the cases autosomal recessive transmission was likely.

The clinical features of the two forms of Kufs' disease delineated above do overlap. Indeed, the mean age of onset and the length of the clinical course of the two types were identical. Type A cases occasionally had extrapyramidal features including tic-like facial dyskinesias which were characteristic of Type B, whereas Type B patients sometimes had seizures. The division into two types is intended to serve as an aid for clinical recognition of Kufs' disease, rather than to imply the presence of two separate diseases.

*Miscellaneous cases*

Table 5 lists cases where there was evidence of abnormal lipopigment storage but the clinical patterns did not conform to either of the clinical groups of Kufs' disease described above.

Six patients can be classified as having the protracted juvenile form. Unlike the classical juvenile form (Spielmeyer-Vogt) where the clinical onset is before the age of 10 yrs (mean 7 yrs) and death occurs before the age of 25 yrs (Sjögren, 1931; Zeman *et al.*, 1970), the protracted juvenile cases had their first symptoms in the second decade and survived until 32 to 52 yrs of age (Table 5). Both the classical and protracted juvenile forms have clinical features of visual failure with retinal degeneration, motor deficits, dementia and seizures. The distinction from Kufs' disease is made on the basis of blindness and pigmentary retinal degeneration which was not present in any of the 50 cases of Kufs' disease reviewed above (Tables 3, 4). This clinical distinction has a pathological correlate; in Kufs' disease there may be storage in retinal ganglion cells with little or no storage in deeper layers of the retina (Kufs, 1929; Greenfield, 1951; Dom *et al.*, 1979), whereas in the juvenile form there is severe involvement of the deep layers with loss of rods and cones resulting in blindness with relative sparing of the ganglion cell layer (Zeman, 1976; Libert *et al.*, 1982).

The second group comprises cases that are difficult to classify, but have been regarded as Kufs' disease because visual failure was absent, although clinical onset was in childhood (Table 5). The siblings described by Dal Canto *et al.* (1974) had unequivocal ultrastructural evidence of NCL, but the clinicopathological picture was very atypical. Clinical onset was with chorea in the 'juvenile' age range and brain biopsy showed curvilinear bodies which are highly characteristic of the late-infantile form (Dal Canto *et al.*, 1974). The relationship of this family to the defined childhood forms of NCL is not clear, but we regard it as quite unhelpful to include this family under the rubric of Kufs' disease. The patients of Walter (1918), Jervis (1950) and of Wakutani *et al.* (1967) had childhood onset of dementia and motor difficulty without visual involvement or seizures. The histological features were

TABLE 5 DEFINITE OR POSSIBLE CASES OF NEURONAL CEROID-LIPOFUSCINOSIS WITH ATYPICAL CLINICAL FEATURES

| *Authors* | *Onset* (*yrs*) | *Death** (*yrs*) | *Clinical features* | *Comment* |
|---|---|---|---|---|
| Protracted juvenile form | | | | |
| Ebhardt *et al* (1973) | 14 | 52 | Blindness, dysarthria, seizures, ataxia, dementia | Pathology based on rectal macrophages which may be unreliable. Case accepted as clinical picture is typical |
| Goebel *et al* (1976) | 10<br>? | 35<br>36† | Two affected sibs, blindness, seizures, dementia | Fingerprint profiles |
| Libert *et al* (1982) | 18<br>16 | 32<br>21*† | Two affected sibs, seizures, blindness, ataxia, myoclonus | Fingerprint profiles |
| Ikeda *et al* (1984) | 20 | 52 | Blindness, psychosis, rigidity, dementia, seizures, myoclonus | Light microscopy consistent with NCL Ultrastructural illustrations not diagnostic |
| Early onset cases without visual involvement | | | | |
| Walter (1918) | 2<br>6<br>1 | 23<br>24*†<br>29*† | Three affected sibs, mental retardation, progressive dementia, motor signs | Light microscopy only |
| Jervis (1950) | 7<br>9<br>10<br>3 | 35<br>22†<br>25†<br>21† | Four affected sibs, dementia, spasticity | Light microscopy only |
| Wakutani *et al.* (1967) | 7 | 37 | Dementia, dyskinesias, dysarthria, ataxia, tremor, increased reflexes | Light microscopy consistent with NCL. Ultrastructure not shown |
| Dal Canto *et al* (1974) | 6.5<br>7 | 10.5*<br>8.5*† | Two affected sibs, dementia, chorea, seizures, ataxia, dysarthria | Typical curvilinear bodies |
| Carpenter *et al* (1977) | 10<br>13 | 38*<br>36* | Two affected sibs, spastic ataxia, pseudobulbar palsy, normal intellect | Fingerprint profiles in skin but not in appendiceal neurons |
| Wisniewski *et al* (1985) | 8.5<br>10.5 | 24*<br>18* | Two affected sibs, spinocerebellar syndrome, neuropathy Another sibling had proven juvenile NCL | Fingerprint profiles described in skin (no illustration). |
| Families with dominant inheritance and protracted course | | | | |
| Dumon-Radermecker (1965) childhood onset | | 70<br>76<br>67 | Autosomal dominant, as many as 15 affected in 3 generations, 3 cases described in detail, onset in childhood with mental retardation and seizures, progressive ataxia, tremor and dysarthria in late life. | Light microscopy only |
| van Bogaert (1961, 1962) | 40<br>20<br>?<br>? | 70†<br>?†<br>26<br>32 | Autosomal dominant, 7 affected in 3 generations (family 'Da'), variable age of onset, ataxia, dementia, myoclonus, seizures, kyphoscoliosis | Light microscopy only |

* Indicates patient still alive at time of report † No pathological data, diagnosis based on affected relatives

consistent with NCL, but ultrastructural studies were not performed or inadequate and the nosological place of these cases is uncertain. Two siblings whom we have briefly noted previously (Carpenter *et al.*, 1977) have clinical features of a slowly progressive spastic ataxia and pseudobulbar palsy without dementia, seizures or sual involvement. Skin biopsy showed fingerprint profiles in the eccrine secretory cells of both cases, but appendiceal neurons did not show evidence of storage. Brain tissue has not been studied in this family, and because of the unusual clinical presentation we remain circumspect about classifying this family as a definite example of Kufs' disease. Similar comments apply to the remarkable siblings described by Wisniewski *et al.* (1985) with a spinocerebellar syndrome, neuropathy, elevated urinary dolichols and fingerprint inclusions in skin and cutaneous nerve.

Finally, there are 2 families with apparently autosomal dominant inheritance and very unusual features (Table 5). Affected members of the family described by Dumon-Radermecker (1965) had symptoms of mental impairment and seizures in childhood with progressive ataxia, dementia and extrapyramidal signs in middle age and a normal life span. Members of the 'Da' family reported by van Bogaert (1961, 1962) had various combinations of ataxia, mental impairment, seizures and kyphoscoliosis with variable age of onset and prolonged survival. The atypical clinical features, together with the absence of ultrastructural data, preclude meaningful classification of these 2 families.

### *Neuropathology*

Brain weight, when stated, ranged from 900 g (Ishino *et al.*, 1972) to 1330 g (Allegranza, 1956) with a mean of 1150 g. This compares to brain weights of 800–1200 g for the juvenile form and 500–700 g for the late infantile type of NCL (Zeman, 1976).

The regional intensity of storage differed from case to case but, in virtually all reports, there was some involvement of the cerebral cortex, basal ganglia and cerebellum. This accords well with the major clinical features of dementia, seizures, movement disorders and ataxia. There were no apparent differences in the distribution of storage material when the two clinical types of Kufs' disease were compared.

The cerebral cortex was always involved; sometimes storage and neuronal loss were limited to layers III and V, whereas in other cases all layers were affected. The occipital cortex tended to be relatively spared whereas the hippocampus was usually heavily involved. In some cases all neurons in an area contained storage, whereas in others a single field might show one neuron distended with granules while an adjacent neuron was spared. Astrocytes were involved in addition to neurons in some reports. The basal ganglia, thalamus, subthalamic nucleus, substantia nigra, pontine nuclei and inferior olive were usually involved. In the cerebellum, variable involvement with neuronal loss and storage was reported in the dentate nucleus and in the Purkinje and granule cell layers (Kufs, 1925, 1929, 1931; Hallervorden, 1938a; Friedrich, 1938; van Bogaert, 1952; Fattovich, 1954; Allegranza, 1956; Seitelberger and Nagy, 1958; Pallis *et al.*, 1967; Boehme *et al.*, 1971; Ishino *et al.*, 1972; Goebel *et al.*, 1982; Tobo *et al.*, 1984).

The spinal cord, when studied, was usually not heavily involved. Storage in anterior horn cells was most often noted, but these cells normally accumulate considerable amounts of lipofuscin (Boehme *et al.*, 1971; Jakob and Kolkmann, 1973; Dom *et al.*, 1979). Involvement of peripheral nerves was not observed (Dom *et al.*, 1979). Retinal storage was largely confined to the ganglion cell layer (Kufs, 1929; Greenfield, 1951; Dom *et al.*, 1979).

Accumulation of extraneuronal pigment in association with neuronal lipid storage may occur and has been termed the 'pigment variant of Kufs' disease'. The severity of the pigment deposition led to confusion with Hallervorden-Spatz disease, although the presence of lipid storage excludes that diagnosis (Dooling *et al.*, 1974). Eight cases of the so-called 'pigment variant' have been published, and they are clearly heterogeneous. We regarded 2 cases as examples of a gangliosidosis or mucolipidosis (Jervis, 1952; Zeman and Scarpelli, 1958); 1 had the action myoclonus-renal failure syndrome (Horoupian and Ross, 1977), 2 did not have clear evidence of lipid storage (Jervis and Pullarkat, 1978; Galatioto *et al*, 1985), 2 had unclassifiable lipidoses (Moschel, 1954; Seitelberger and Simma, 1962) and 1 probably had Kufs' disease (Jakob and Kolkmann, 1973). The cause of the occasional association of intense extraneuronal pigmentation with diverse forms of neuronal lipidosis is not apparent. These cases do not, however, represent a discrete clinicopathological syndrome, and the use of the term 'pigment variant of Kufs' disease' should be abandoned.

### *Visceral pathology*

Visceral involvement was never macroscopically apparent. In the carefully studied case of Kufs (1925), there was prominent microscopic involvement of renal tubules, hepatocytes, Kupffer cells, macrophages, thyroid, heart, pancreas, and blood vessels. Unfortunately, the extent of microscopic involvement has not been as extensively evaluated in other cases. Minor and inconstant evidence of storage has been reported in heart muscle, hepatocytes, renal tubules, macrophages and intestinal mucosa (Pallis *et al.*, 1967; Dom *et al.*, 1979; Goebel *et al.*, 1982). Involvement of skin may sometimes be suspected from semithin sections; electron microscopy shows inclusions in the eccrine secretory cells (fig. 6). In many cases of Kufs' disease, storage is not present in all neurons; this fact suggests that visceral storage in such cases may also be quite restricted. Only thorough postmortem investigations with light and electron microscopy will give us adequate data on this point.

## DISCUSSION

Kufs' disease is rare. We accepted the diagnosis in 50 published cases (Tables 3 and 4) from a total of 118 cases reviewed. Unfortunately, even amongst these 50 cases, only a minority fulfilled the most definitive criterion for diagnosis, that of the ultrastructural demonstration of fingerprint profiles or GRODs in the presence of consistent light microscopic findings. We elected to accept those other cases, including the reports of Kufs himself, where ultrastructural data were unavailable or inadequate, but where light microscopic data were highly suggestive of the diagnosis. Although this approach is open to criticism, we believe that analysis of these 50 cases presents a more complete view of the disorder than would otherwise be possible. The validity of this view will only be determined with the publication of further cases with ultrastructural data and, eventually, with the correlation of primary biochemical defects with clinicopathologic phenotypes.

### *Clinical features*

Kufs' disease has an equal sex incidence. The mean age of clinical onset is 29.7 ± 10.1 yrs (range 11–50 yrs) and the mean length of the illness is 12.5 ± 8.1 yrs. Two main clinical presentations occur.

The more common clinical phenotype is of progressive myoclonus epilepsy, with symptoms typically beginning around the age of 30 yrs (Table 3). At onset, diagnosis is difficult, especially if myoclonus and dementia are not prominent, and the patient is usually regarded as having a benign form of generalized epilepsy of late onset. Suspicion of a progressive degenerative disease should be aroused when seizures become intractable or when signs of dementia and ataxia develop. Intractable generalized epilepsy with onset in adult life is extremely unusual in the absence of obvious causative or triggering factors such as a severe head injury, encephalitis, alcohol abuse or a toxic encephalopathy, and a progressive disorder such as Kufs' disease should be suspected. Rather few other disorders are known to cause progressive myoclonus epilepsy with onset around the age of 30; they include mitochondrial encephalomyopathies, sialidosis type II, dentatorubro-pallidoluysian atrophy, atypical inclusion body disease, and the very rare late forms of Lafora body disease and of Gaucher's disease (Berkovic and Andermann, 1986). Prolonged generalized convulsions, marked photosensitivity and visual auras are clinical clues that may suggest Kufs' disease, but there are insufficient data to determine the sensitivity and specificity of these clinical features. Kufs' disease may also present with progressive myoclonus epilepsy in adolescence (fig. 8); here the differential diagnosis is more extensive and the clinical approach to this problem is outlined elsewhere (Berkovic *et al.*, 1986).

The less common clinical presentation of Kufs' disease is of behaviour change and dementia in association with motor disturbances. Movement disorders, particularly dyskinesias around the face, are common. Dysarthria and ataxia are also frequent features (Table 4). The differential diagnosis of dementia presenting at this age is extensive and well known (Marsden, 1985) and only a few comments are warranted. Wilson's disease and Huntington's disease must be excluded in the setting of dementia and movement disorder. Alzheimer's disease has a prevalence many orders of magnitude higher than Kufs' disease, but its incidence in the 25–45 year old age group is very low (Rocca *et al.*, 1986), and a presentation with motor disturbances rather than a true 'cortical' dementia would be unusual. Creutzfeldt-

Jakob disease could possibly mimic either of the clinical forms of Kufs' disease but, unlike Kufs' disease, it usually begins after the age of 45 yrs and the clinical course is much more rapid (Brown *et al.*, 1979).

Both types of Kufs' disease are notable for the absence of blindness and of pigmentary retinal degeneration. In view of the finding of storage material in retinal ganglion cells, Dom *et al.* (1979) suggested that some visual impairment might occur terminally but that it remains undetected due to severe dementia. Sensory abnormalities are never seen, and amyotrophy only occurs due to terminal cachexia. Pyramidal signs are usually inconspicuous, although rigidity of extrapyramidal type may occur.

### *Clinical limits of Kufs' disease*

Kufs' disease is largely a disease of early and middle adult life. Cases of NCL with onset in adolescence lie at the interface between classical juvenile and adult NCL. The adolescent cases fall into two main groups. First, there are 6 published cases with visual failure and pigmentary retinal degeneration (Table 5). These cases clearly differ from Kufs' disease and are regarded as the protracted juvenile subgroup. Secondly, there are 9 adolescent cases whose clinical features otherwise resemble adult Kufs' disease (Tables 3, 4). The two clusters of age of onset of Kufs' disease, in early adolescence and around the age of 30 yrs (fig. 6), suggest that adolescent and adult Kufs' disease may be separate entities, although the occurrence of adolescent and adult cases in two families (Kufs, 1925, 1929; van Bogaert and Borremans, 1937; van Bogaert, 1952, 1962) argues against this. At present, we regard these 9 adolescent cases without visual failure as part of the spectrum of Kufs' disease. The clinical and pathological features of juvenile NCL, protracted juvenile NCL and Kufs' disease are contrasted in Table 6.

Twenty-one cases remain which are difficult to classify; there are the atypical early onset cases without visual involvement, and the unusual families with dominant inheritance and protracted course (Table 5). These cases are too clinically heterogeneous and insufficiently characterized pathologically to propose additional categories at present. We regard these cases as outside the spectrum of Kufs' disease; they may represent peculiar allelic variants of NCL, or be examples of other uncharacterized disorders.

### *Electrophysiology*

The resting EEG shows nonspecific changes; slowing of background rhythm may occur in both phenotypes and generalized spike-wave discharges are seen in the progressive myoclonus epilepsy (Type A) phenotype. The intense photoparoxysmal response and the unusual sensitivity to low frequency photic stimulation seen in the family reported here (fig. 2) may, however, be of diagnostic significance. Marked photosensitivity in adult onset epilepsies is very unusual, and responses to flash frequencies of 1–2 Hz are extraordinary (Newmark and Penry, 1979). The patients of Pallis *et al.* (1967) and Vercruyssen *et al.* (1982) were also photosensitive, but

TABLE 6 COMPARISON OF JUVENILE NCL, PROTRACTED JUVENILE NCL AND KUFS' DISEASE*

| | *Juvenile NCL* | | *Late onset NCL* | |
|---|---|---|---|---|
| | *(Spielmeyer-Vogt)* | *Protracted juvenile NCL* | *(Kufs)* | |
| Reported cases | >300 | 6 | 50 | |
| Age of onset (yrs) | | | | |
| Mean | 7±1.1 | 15±3 | 30±10 | |
| Range | 4–10 | 10–20 | 11–50 | |
| Main clinical features | | | Type A | Type B |
| | Blindness<br>Pigmentary retinal degeneration<br>Seizures<br>Dementia<br>Rigidity | Blindness<br>Pigmentary retinal degeneration<br>Seizures<br>Dementia | Seizures<br>Myoclonus<br>Dementia<br>Ataxia<br>Normal vision | Dementia<br>Facial dyskinesias<br>Ataxia<br>Normal vision |
| Ultrastructure of lipopigment | | | | |
| | Fingerprint profiles<br>GRODs (rare) | Fingerprint profiles | Fingerprint profiles or GRODs | |

* Data on juvenile NCL based on Sjogren (1931), Zeman *et al* (1970), Carpenter *et al* (1973, 1977) and Santavuori *et al* (1985) Data for protracted juvenile NCL derived from Table 5 and for Kufs' disease from Tables 3 and 4

detailed EEG data were not published. The case of Aihara *et al.* (1976) had a seizure following photic stimulation at 3 Hz. Further patients must be studied to determine whether photosensitivity at low frequency stimulation is a common feature in Type A Kufs' disease. The only other disorder where this phenomenon is regularly seen is the late infantile type of NCL, although in that condition the occipital spikes are usually even more prominent and correlate with a giant visual evoked response (Pampiglione and Harden, 1977). The observation of this unusual photic response in two separate forms of NCL suggests that the storage process may have a similar effect on the neural generators of photosensitivity in both conditions.

Visual evoked responses and brainstem auditory evoked responses are normal in Kufs' disease (Vercruyssen *et al.*, 1982). Giant short-latency somatosensory evoked potentials (SEPs) may be observed (Vercruyssen *et al.*, 1982), although they were not present in our family. Giant SEPs are a finding common to many forms of progressive myoclonus epilepsy (Shibasaki *et al.*, 1985) and are not of value in differential diagnosis.

The photopic electroretinogram (ERG) is sensitive to disease of the deeper retinal layers and the b wave is often abolished in the infantile, late infantile and juvenile forms of NCL (Pampiglione and Harden, 1977). The photopic ERG was preserved in our cases and in the patients of Vercruyssen *et al.* (1982). Dawson *et al.* (1985) reported that the b waves were reduced, delayed and showed pronounced oscillations in 2 cases. The interpretation of these findings is difficult, especially in view of the very atypical clinical features of their second case and of the inadequate pathological documentation of Kufs' disease in both cases, with only low magnification electron micrographs. The pattern ERG may be sensitive to disease of the outer retinal layers, and thus could be of more value in Kufs' disease. We found a normal pattern ERG in Case 2, whereas Vercruyssen *et al.* (1982) reported an unspecified decrease in b wave amplitude in one case. Further studies are needed, but we doubt if photopic or pattern ERG will be of value in the diagnosis of Kufs' disease.

### *Urinary sediment dolichols*

Urinary sediment dolichol levels are elevated in the infantile, late infantile and juvenile forms of NCL. False negative results occur in 7 to 15% of cases, but usually become positive on repeat testing. False positive results are seen in about 15% of age-matched normal children and children with other neurological diseases. Known causes of false positive results include strenuous exercise, urinary tract infection, menstrual fluid contamination, Hermansky-Pudlak syndrome, Niemann-Pick disease group II, and I cell disease (Wolfe *et al.*, 1983, 1986*a*, *b*).

Markedly elevated levels were found in the 2 affected patients in this report. Levels were normal in the unaffected parents, offspring, and in 2 of the 3 siblings (Table 1). A larger series is required to establish the sensitivity of this test for Kufs' disease. Elevated urinary sediment dolichol levels in adulthood are not absolutely specific for Kufs' disease because, although levels do not rise with age, and they are normal in Alzheimer's disease, elevated levels can occur in certain incompletely characterized adult dementias and in Creutzfeldt-Jakob disease (Mandell *et al.*, 1985; Wolfe *et al.*, 1985, 1986, 1987). The finding of elevated urinary sediment dolichol levels in a clinically possible case of Kufs' disease should lead to a careful search for diagnostic inclusions by electron microscopy. Elevated dolichol levels must not be regarded as diagnostic of Kufs' disease in cases where pathological studies are equivocal.

### *Pathology*

Careful pathological evaluation remains mandatory for the diagnosis of Kufs' disease. Skin biopsy is the simplest and least invasive diagnostic technique but it is essential to use electron microscopy and to examine eccrine secretory cells, duct cells and smooth muscle. Dom *et al.* (1979) initially reported a negative skin biopsy in their Case 2, but when eccrine secretory cells were studied, diagnostic fingerprint profiles were seen (Vercruyssen *et al.*, 1982). Skeletal muscle biopsy may be diagnostic in some cases (Dom *et al.*, 1979) but it was negative in our Case 1 and, by analogy to the juvenile type where skeletal muscle storage is not invariable (Carpenter *et al.*, 1977), we do not recommend reliance on muscle biopsy for diagnosis. Neurons in rectal biopsy specimens may also be positive (Dom *et al.*, 1979), but there is insufficient experience with this technique in Kufs' disease to tell whether negative findings rule out the diagnosis. Brain biopsy is reliable providing a full thickness cortical biopsy is taken, as storage may be limited to the large neurons in the third and fifth cortical layers.

The importance of careful ultrastructural studies cannot be overemphasized.

Fingerprint profiles are unfortunately not completely specific for NCL. In rodents they occur in normal neurons; in man they occur nonspecifically in smooth muscle cells of renal arterioles. We have found a few fingerprint profiles in eccrine secretory cells of 3 other cases who did not appear to have NCL. The diagnosis of NCL from skin is reasonably certain only if they are found in more than one cell type in a biopsy. Fingerprint profiles diagnostic of Kufs' disease were clearly seen in autopsy or biopsy material in the cases of Aihara *et al.* (1976), Greenwood and Nelson (1978), Vercruyssen *et al.* (1982), Case 1 of Goebel *et al.* (1982), and the 2 cases reported here. A number of other reports described fingerprint profiles, but the illustrations were not entirely convincing. The cases of Kufs' disease with GRODs include those of Boehme *et al.* (1971) and Dekaban and Herman (1974). The difficulties in distinguishing GRODs from normal lipofuscin have already been discussed, and this is especially true when assessing published reports as the data available for evaluation are, of necessity, limited. Nevertheless, we found the illustrations in the aforementioned cases sufficiently convincing to regard GRODs as an alternate form of lipopigment storage to the firmly established occurrence of fingerprint profiles. Finally, it should be noted that the diagnostic deposits of NCL may be seen alongside ordinary lipofuscin in Kufs' disease.

### *Genetics*

Of the 50 cases of Kufs' disease, 34 were familial and 16 were apparently sporadic (Tables 3, 4). Autosomal recessive inheritance was likely for the majority of cases because of recurrence in siblings, absence of affected parents or other relatives, and increased parental consanguinity. In two families (Boehme *et al.*, 1971; Ferrer *et al.*, 1980), each representing one of the main clinical phenotypes, autosomal dominant inheritance was observed. The possibility of pseudodominance, due to extensive inbreeding, was not rigorously excluded, but was unlikely. The expression of separate autosomal dominant and recessive genotypes as an identical clinicopathological phenotype is very unusual, and is further discussed below.

Kufs' disease is found in a number of ethnic and racial groups including Anglo-Saxons, northern and southern Europeans and Japanese. Jewish ancestry was not mentioned in any of the reports of Kufs' disease. Although certain storage disorders have an increased incidence in Jews, particularly the classical and adult forms of $G_{M2}$ gangliosidosis, the early forms of NCL are extremely rare in Jews, and it now seems that the same is true of the adult form. Jewish ancestry was, however, described in a number of cases where we rejected the diagnosis of Kufs' disease (Moschel, 1954; Fine *et al.*, 1960; Jervis and Pullarkat, 1978) and in the family 'Da' of van Bogaert (1962) which was unclassifiable. This perhaps represents independent genetic evidence that our classification of these cases, based largely on pathological criteria, is valid and that the anomalous cases do represent examples of other disorders such as the gangliosidoses.

There is no evidence of a genetic link between the infantile, late infantile and juvenile subgroups of NCL. Even in geographical regions where two subgroups are found side by side with a high prevalence, such as Newfoundland (late infantile and early juvenile variant) and Finland (infantile and juvenile), family studies suggest that the subgroups are quite distinct since more than one phenotype was never found in the same sibship (Andermann *et al.*, 1977; Carpenter *et al.*, 1977; Rapola *et al.*, 1984). Similarly, none of the 50 cases of Kufs' disease reviewed here had relatives described with early forms of NCL. According to Lake (1984), and in our own view, reports describing affected adults in families with early forms of NCL (Edgar and Post, 1963; Perris and Strandqvist, 1969; Kamijyo *et al.*, 1974; Badurska *et al.*, 1981; Clayton and Schiffman, 1986) can be discounted, as the pathological material did not show evidence of abnormal lipopigment storage and the clinical courses were quite atypical for Kufs' disease. The only family warranting serious consideration is that of Zeman and Hoffman (1962). In that consanguineous family, with a high incidence of neurological and visual deficits, two siblings had typical juvenile NCL and a distant paternal cousin had a peculiar biphasic illness beginning at the age of 18 yrs and terminating in death at age 53 with dementia, ataxia, retinal pigmentation and seizures. Unfortunately, the brain was poorly fixed, and it is difficult to be certain that there was abnormal storage. While it is possible that this patient had Kufs' disease, there are clinical and pathological reasons to doubt this, and the case certainly does not establish a genetic link between the juvenile and adult forms of NCL.

### *Biochemistry and aetiology*

The biochemistry of Batten-Kufs' disease is poorly understood. Zeman and coworkers introduced the term 'neuronal ceroid-lipofuscinosis', which reflected their concept that ceroid was stored in the early forms of NCL and that lipofuscin (age pigment) was stored in Kufs' disease (Zeman and Dyken, 1969; Zeman *et al*, 1970; Zeman, 1976; Siakotos and Munkres, 1982). The term NCL has been widely accepted, but the underlying concept can be criticized. First, there does not appear to be any consistent difference between ceroid and lipofuscin using histological, chemical and spectroscopic criteria. Secondly, although the abnormal lipopigment in NCL can be considered as a form of ceroid, it differs from the ceroid of other disorders in certain microscopic ultrastructural, histochemical and spectroscopic aspects (Carpenter *et al.*, 1973, 1977; Dowson, 1982; Lake, 1984; Sohal and Wolfe, 1986). Thirdly, the view that the storage material in the early forms differs from that in Kufs' disease is not tenable. This view was initially based on the ultrastructural finding of fingerprint profiles in the juvenile form and of GRODs in Kufs' disease (Zeman, 1976). It is now known that GRODs may occur, albeit rarely, in juvenile cases (Carpenter *et al.*, 1973; Lake, 1984) and that both types of deposit also occur in Kufs' disease (Table 6).

The abnormal lipopigment consists primarily of insoluble proteins with 20 to 40% lipid. Dolichols account for up to 5%. The autofluorescence may be due to retinoyl complexes which are present in only tiny quantities (Wolfe *et al.*, 1977, 1983, 1986*b*). The storage material, like normal lipofuscin, is found in secondary lysosomes, and probably is largely derived from indigestible components of intracellular membranes (Sohal and Wolfe, 1986). It is likely that the metabolic defects in NCL are related to the system that normally processes lipofuscin. Defects in the system would account for the qualitative and quantitative differences between the storage material and normal lipofuscin, and for the fact that the storage damages neurons, whereas normal lipofuscin does not (Wolfe *et al*., 1986*b*).

The nature of the enzyme defects in NCL are unknown. An early hypothesis suggested that there was increased oxidation of polyunsaturated fatty acids, possibly due to a deficiency of specific peroxidase enzymes, with cross linking of proteins due to generation of malondialdehyde (Chio *et al*., 1969; Zeman, 1976). There is now much evidence against this hypothesis (Wolfe *et al*., 1987). The finding of increased levels of dolichols in the brain and urinary sediment of patients with NCL has focused attention on the lysosomal membrane, as dolichols are concentrated there. Wolfe *et al*. (1987) have suggested that the basic defects may lie in the enzymes responsible for the catabolism, recycling or exocytosis of intracellular membranes, particularly those associated with lysosomes. Candidate enzymes include the thiol endoproteases. Support for this view comes from experiments showing that inhibition of thiol endoproteases, but intracerebroventricular infusion of leupeptin or chloroquine, leads to accumulation of lipopigments and of dolichols (Ivy *et al*., 1984; Wolfe *et al*., 1987).

In NCL a series of defects in the metabolism of lysosomal or Golgi membranes can be envisaged, leading to the differential effects on various cell types and the characteristic ages of onset of the various clinical subgroups. The ultrastructural morphology of the lipopigment deposits probably depends on their lipid content, and the different ultrastructural formations may reflect specificity in the classes of intracellular membranes affected by different enzyme defects in the various subgroups. Such specificity would also explain why normal lipofuscin may be seen in the same cells as abnormal lipopigment in these disorders.

The finding of both dominant and recessive modes of transmission in one condition should engender scepticism, but we think the case for this in Kufs' disease is fairly strong. This implies heterogeneity in the molecular mechanisms of this rare form of NCL. If the biochemical defects involved a system with a complex series of subunits and regulator proteins, it is conceivable that a recessive gene resulting in deficiency of a protein could have the same effect as a dominant gene which could disrupt the system at a regulator step. Alternatively, a dominant gene may cause an effective total deficiency of a multisubunit protein by the mechanism of 'protein suicide', as has been shown in a form of osteogenesis imperfecta (Prockop and Kivirikko, 1984).

### *Conclusions*

1. Kufs' disease is rare and delineation of its features has been hampered by confusion with other lipidoses of adulthood.

2. Symptoms typically begin around the age of 30 yrs although a small group of cases have onset in early adolescence.

3. Two clinical phenotypes are discernible. Type A presents with progressive myoclonus epilepsy and the differential diagnosis is relatively limited. Type B has symptoms of behavioural change, dementia and motor disturbances. The differential diagnosis is extensive but the presence of facial dyskinesias may be a helpful clinical clue.

4. The clinical course averages 12.5 yrs with death due to dementia. Visual failure does not occur.

5. Noninvasive diagnostic tests that may be of value include elevated urinary sediment dolichol levels and, in the Type A phenotype, a marked photoparoxysmal response on EEG with abnormal responses even at low frequencies of stimulation.

6. Careful pathological evaluation is essential for diagnosis. Ultrastructural studies reveal fingerprint profiles or GRODs. Skin biopsy will show them in eccrine secretory cells but is not diagnostic unless other cell types are seen to be involved.

7. Kufs' disease is clinically and genetically distinct from the early forms of Batten's disease, but it is genetically heterogeneous with both recessive and dominant modes of transmission.

8. The finding of elevated urinary sediment dolichol levels in Kufs' disease is consistent with the hypothesis that the various forms of NCL are due to defects in the intracellular processing of lysosomal membranes.

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# HUMAN SACCADIC EYE MOVEMENTS IN THE ABSENCE OF THE GENICULOCALCARINE PROJECTION

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## SUMMARY

This paper describes the results of an investigation into the spatial and temporal properties of the saccadic eye-movement system in a subject with a 'blind' hemifield caused by accidental damage to the left geniculostriate projection. The results show that blind hemifield stimulation can elicit goal-directed saccades of short latency provided the contrast of the visual stimulus is above the threshold required for saccade generation at the corresponding stimulus eccentricity. Signal processing associated with blind hemifield pathways shows reduced sensitivity by comparison with the normal hemifield and greater dependence on stimulus size, eccentricity and mode of presentation. Higher contrast levels are always needed for blind field stimulation and larger variance in mean saccadic amplitudes and latencies is normally observed. Large stimulus eccentricities which would normally require corrective saccades exhibit a different response pattern to that observed in normal vision. The results show that the centre of gravity effect and the generation of rapid, 'express-saccades' observed in normal vision are not inevitable outcomes of midbrain processing of visual information. The subject's performance reveals strategic patterns of eye-movement responses which maximize the use of his normal hemifield Visual performance in the control of saccadic eye-movement responses appears to be optimum when the detection of the visual stimulus is associated with both the geniculostriate and the midbrain pathways. Experiments designed to test for the effects of light scatter into the normal hemifield show that the subject's saccadic eye-movement performance following visual stimulation of the blind hemifield cannot be attributed either to the amount or the pattern of light scatter into the normal hemifield. The implications of present findings on the results of other studies of eye-movements in subjects with scotomas associated with cortical lesions are also examined.

## INTRODUCTION

The saccadic eye movement system has particular attraction for researchers since it involves a sensorimotor pathway whose function is clear and simple, yet of sufficient complexity to illustrate the information processing properties of neural

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networks. In this paper we present the results of a detailed study of saccadic eye movements in a subject with a 'blind' hemifield caused by accidental damage to the left hemisphere.

Results of physiological and behavioural studies provide considerable support for the view that two separate processes are involved in the generation of a saccade, one (the 'WHEN' system) which initiates the process and the second (the 'WHERE' system) which determines the position in space to which the saccade is directed (Becker and Jürgens, 1979; van Gisbergen *et al.*, 1981; Findlay, 1983; Fuchs *et al.*, 1985). The spatial characteristics of a visually elicited saccade which orients the gaze to a new location in the visual field are computed from visual information about the eccentricity and direction of the target.

The sensorimotor transformation from target position to movement command shows the following unexpected property. When a subject makes a saccadic response to a target consisting of two elements at neighbouring positions in the visual periphery, the saccade lands at an intermediate position rather than on either element even when the elements are clearly resolved perceptually and the subject's intention is to scan the elements sequentially (Findlay, 1982, 1983). It appears that the visual signal coding the target location in the visual field is subject to considerable spatial integration, even though at the retina itself, target position is coded as retinal position. Although a variety of attentional strategies can affect saccade metrics (Findlay, 1985), the 'default' option in the normal saccadic system appears to bring the eye to the light-flux weighted centre of the target (Ottes *et al.*, 1984). Other observations show that saccades with short latencies land near the light-flux weighted centre of the target, whereas saccades with longer latencies are directed progressively nearer to an individual element position in the target (Findlay, 1982).

Combined anatomical and electrophysiological studies show that longer latency saccades are normally associated with ablation of the superior colliculus, whereas the effect of lesions to the visual cortex appears to be a reduction in the accuracy of the movement (Mohler and Wurtz, 1977). Studies in human vision have shown that patients who have sustained loss of part of the geniculostriate pathway can nevertheless make appropriate saccades to targets imaged within the corresponding scotomas (Pöppel *et al.*, 1973; Weiskrantz *et al.*, 1974; Perenin and Jeannerod, 1975; Zihl, 1980). In these reports the saccades appeared to be made in the absence of conscious awareness of stimulation in the scotoma, although the status of this 'blindsight' phenomenon has been questioned (Campion *et al.*, 1983). These studies have, in general, been concerned to establish the existence of spatially appropriate saccades following stimulation of blind areas of the visual field and have not analysed the properties of the responses in further detail. The superior colliculus receives a direct projection from the retina and provides an alternative route which might mediate such saccades. Lesion studies (Mohler and Wurtz, 1977; Schiller *et al.*, 1980) support the view that saccades may be mediated by *either* a collicular *or* a cortical pathway. It has also been suggested that one particular class of saccades with very short latencies, 'express saccades', may be mediated by collicular pathways (Boch *et al.*, 1984; Sandell *et al.*, 1984).

In this study we report the results of an extensive investigation of saccadic eye movements in a subject with a blind hemifield caused by accidental damage to the left cerebral hemisphere. The tests carried out reveal the spatial and temporal properties of his saccades, following visual stimulation of both blind and normal hemifields.

## CASE HISTORY

The subject (G.) was involved in a car accident when 8 yrs old which caused damage to his left hemisphere. Following the accident, he was unable to detect any visual stimuli when images were presented in his blind hemifield and this is consistent with an almost complete right homonymous hemianopia which was diagnosed soon after the accident. A more detailed map of his visual field sensitivity was obtained 14 yrs after the accident and shows some differential sensitivity along the vertical foveal meridian with macular sparing which extends some 2.5° into the blind hemifield (Barbur *et al.*, 1980). G.'s visual field map was reassessed in this study using a dark test stimulus on a bright background field so as to minimize the effect of scattered light. The results are shown in fig. 1 and are virtually unchanged from those obtained in previous tests. Recent CT scans (Blythe *et al.*, 1987) show that the damage caused by the accident has resulted in unilateral destruction of the left striate cortex (fig. 2). Earlier psychophysical investigations (Barbur *et al.*, 1980) have shown that G. can, using a verbal response, localize flashed targets when images are presented in his blind hemifield and can discriminate the direction of movement associated with fast moving targets or sequential flashes which produce apparent motion when presented to a normal subject

## EQUIPMENT AND EXPERIMENTAL METHODS

G. was seated in a fixed clinical chair positioned at a distance of 1 7 m from a concentric cylindrical screen presenting a uniform visual field of width 100° and height 40° His movements were minimized by means of an adjustable padded frame which was attached to the clinical chair and immobilized his head. Eye movements were recorded by means of an infrared binocular eye tracker (Haines Optoelectronic Developments, Model 53). A series of red light-emitting diodes, which were embedded in the screen, were used for fixation and for calibrating the eye tracker.

The test stimuli were circular targets of either 1° or 2° diameter and were presented either singly or in pairs at randomly selected eccentricities. These stimuli were produced by means of a Kodak S-RA-2000 Random Access Carousel Projector with a 93 mm lens, which was placed at a distance of 3 m from the screen, and was fitted with a silent fast response electronic shutter (Forth Instruments Ltd.). The control of the fixation stimulus, together with the test stimulus eccentricity and duration was achieved by means of an Analog Devices Macsym 150 Measurement and Control System The analog signal from the eye tracker was sampled once every millisecond and, following low pass filtering which involved the weighting of 5 sequential samples, the data were converted to absolute units and stored for analysis.

The eye movement monitor was recalibrated at regular intervals after about every 20 presentations of the stimuli A red fixation stimulus of 0.3° diameter was used to maintain steady fixation. Each measurement was preceded by an initial test of eye tracker signal so as to ensure appropriate steady fixation If a fixation error was detected, the measurement was delayed and this was indicated to the subject by means of an intermittent tone and by flashing the fixation light

A second carousel projector, fitted with a 36 mm lens, provided uniform background illumination over the screen. The luminances of the test stimuli, the background field and the fixation lights were

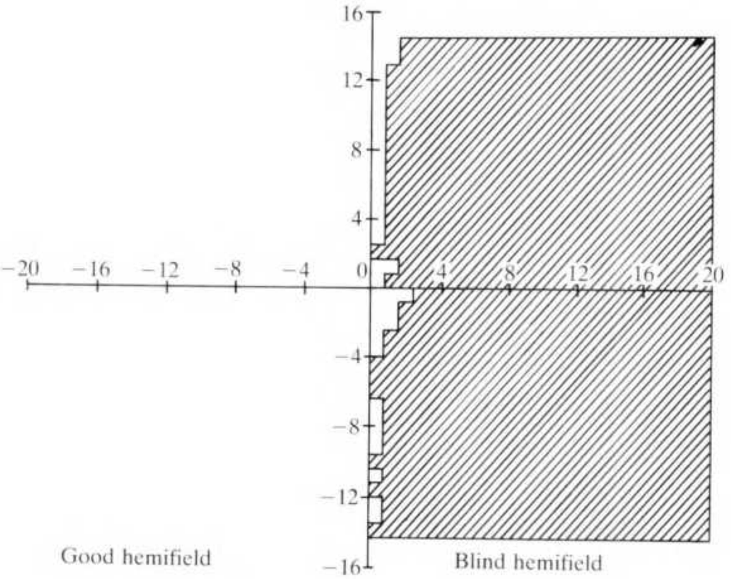


FIG. 1. Perimetric plot of visual sensitivity for Subject G. The results were obtained with the right eye and fixation was monitored continuously throughout the experiment by means of a Haines eye-tracker unit. The perimetry programme was implemented on a high resolution graphics display with good control of test target luminance and location in the visual field. The square test stimulus was of negative contrast (i.e., 12 cd/m$^2$ against a uniform background of luminance 109 cd/m$^2$) and subtended a visual angle of 0.8° × 0.8°. Macular sparing extends some 2.5° into the blind hemifield (i.e., the shaded area to the right).

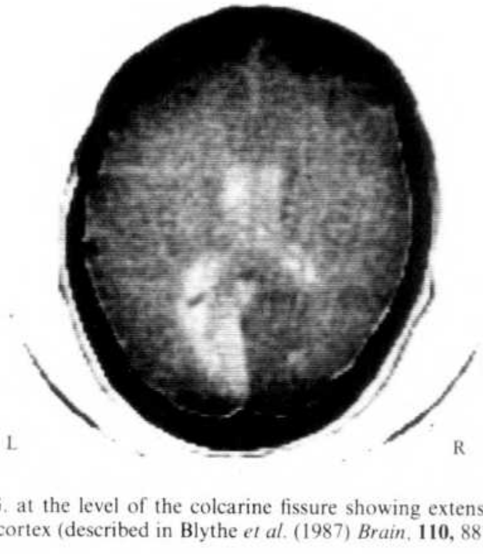


FIG. 2. CT scan of subject G. at the level of the colcarine fissure showing extensive unilateral damage to the striate cortex (described in Blythe *et al.* (1987) *Brain*, **110,** 887–905.

measured with an LMT Model 1000 luminance meter. The values used in these experiments were: background, 9.5 cd/m², fixation lights 23 cd/m², test stimuli 139 cd/m² (except where otherwise stated).

Each experimental run lasted about 20 min, during which time it was possible to present 6 different test stimuli, 10 times each, in a randomized order

The eye movement records were later retrieved from disc storage, and analysed by locating the beginning and end of the first saccade, either automatically using a simple algorithm for saccade detection which triggered whenever the eye velocity exceeded 40 deg/s or, for unusual responses, by guiding the screen cursor visually and recording the appropriate coordinates From such coordinates the response latency, saccade velocity and saccade amplitude were calculated. Between 2 and 5 runs were made of each experimental condition, so that any one stimulus was presented and analysed between 20 and 50 times. Histograms were generated and means and SDs were calculated for the latencies and amplitudes of the saccades. Four normal observers also participated in these measurements and were used to carry out control runs for some of the experiments.

### *Summary of presentation conditions*

*Stimulus Condition 1.* The test target was presented randomly at the selected eccentricity along the horizontal meridian and remained on the screen until a response was recorded. *The fixation light was switched off 200 ms before target onset.*

*Stimulus Condition 2.* This was the same as Stimulus Condition 1, but *the offset of the fixation stimulus was simultaneous with the target onset.* The target was then displayed until a response was recorded.

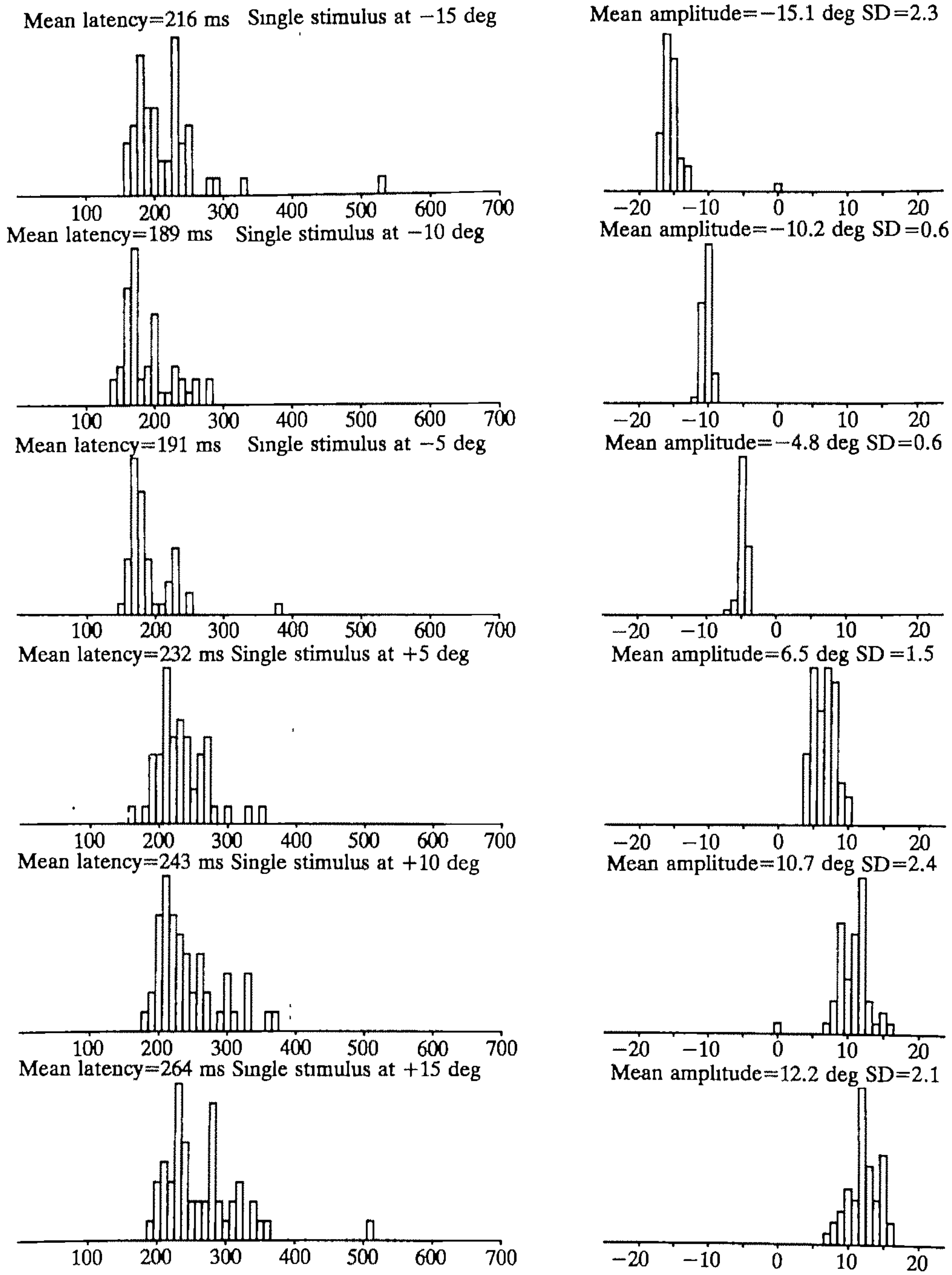
*Stimulus Condition 3* This was the same as Stimulus Condition 2, but the *test target was presented as a 160 ms flash* The offset of the fixation point was simultaneous with the onset of the target

## RESULTS

### *Experiment 1*

This experiment was designed for the investigation of G.'s basic saccadic eye movement response following stimulation of his blind and normal hemifields. Six stimulus eccentricities were used. The stimulus was a disc of 2° diameter and was presented under three different conditions at eccentricities of 5°, 10° and 15° in each hemifield.

The results of this experiment are presented in Table 1 and were calculated from data similar to those shown as frequency response histograms in fig. 3. The relationship between saccade mean amplitude and stimulus eccentricity for the hemianope and for a normal subject is shown graphically in fig. 4A, B. The results of fig. 4 were obtained using Stimulus Condition 3. In this condition the offset of the stimulus flash quite often precedes the onset of the saccade. The hemianope shows accurate responses for both good and blind hemifield stimulation with the stimulus presented at 5° and 10° eccentricity, but he quite often undershoots in response to the 15° target in the blind hemifield. Saccadic undershoot is a frequently observed phenomenon and the saccades of the normal subject in fig. 3B also show it. Saccade latencies tended to be longer in response to blind field stimulation although significant differences between the two hemifields were also observed with normal subjects (*see* Table 1, Stimulus Condition 1, Subject J.B.). The flashed


Mean latency=216 ms Single stimulus at −15 deg

Mean amplitude=−15.1 deg SD=2.3

Mean latency=189 ms Single stimulus at −10 deg

Mean amplitude=−10.2 deg SD=0.6

Mean latency=191 ms Single stimulus at −5 deg

Mean amplitude=−4.8 deg SD=0.6

Mean latency=232 ms Single stimulus at +5 deg

Mean amplitude=6.5 deg SD=1.5

Mean latency=243 ms Single stimulus at +10 deg

Mean amplitude=10.7 deg SD=2.4

Mean latency=264 ms Single stimulus at +15 deg

Mean amplitude=12.2 deg SD=2.1

FIG. 3. Eye-movement frequency response histograms showing the distribution of response latencies and amplitudes The stimulus was a 2° diameter disc and was presented randomly at one of six discrete eccentricities. The data were obtained for Subject G using Stimulus Condition 2.

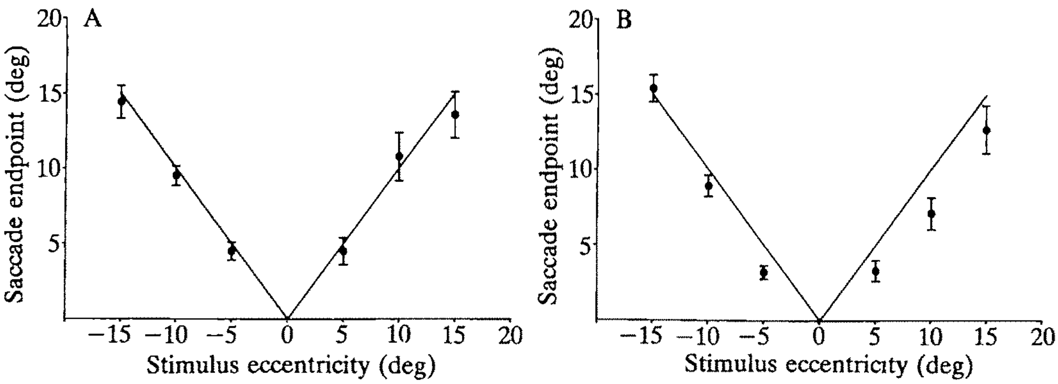


Fig 4 Summary of mean saccade amplitude plotted against stimulus eccentricity. The results were obtained using Stimulus Condition 3. a, Subject G., b, Subject J.B

TABLE 1 RESULTS OF EYE-MOVEMENT MEASUREMENTS CALCULATED FROM HISTOGRAM DATA SIMILAR TO THOSE OF FIG 1, FOR TWO SUBJECTS AND THREE STIMULUS CONDITIONS

| Eccentricity (deg) | −15 | −10 | −5 | 5 | 10 | 15 |
|---|---|---|---|---|---|---|
| Stimulus Condition 1 | | | *Subject G* | | | |
| Mean amplitude (deg) | −14.5 | −10.3 | −5.1 | 5.9 | 9.8 | 11.2 |
| SD | 1.4 | 0.7 | 0.5 | 1.6 | 1.6 | 2.3 |
| Mean latency (ms) | 174 | 171 | 207 | 180 | 175 | 201 |
| Stimulus Condition 1 | | | *Subject J B* | | | |
| Mean amplitude (deg) | −15.7 | −10.1 | −5.2 | 5.1 | 8.2 | 15.2 |
| SD | 2.2 | 1.9 | 1.1 | 1.1 | 1.9 | 3.2 |
| Mean latency (ms) | 236 | 216 | 223 | 183 | 139 | 188 |
| Stimulus Condition 2 | | | *Subject G* | | | |
| Mean amplitude (deg) | −15.5 | −10.2 | −4.8 | 6.5 | 11.0 | 12.2 |
| SD | 1.0 | 0.6 | 0.6 | 1.5 | 1.9 | 2.1 |
| Mean latency (ms) | 216 | 189 | 191 | 232 | 242 | 264 |
| Stimulus Condition 2 | | | *Subject J B* | | | |
| Mean amplitude (deg) | −17.2 | −10.8 | −5.4 | 4.7 | 9.1 | 14.1 |
| SD | 1.2 | 1.0 | 0.5 | 0.6 | 1.1 | 1.8 |
| Mean latency (ms) | 270 | 266 | 286 | 194 | 255 | 290 |
| Stimulus Condition 3 | | | *Subject G* | | | |
| Mean amplitude (deg) | −14.4 | −9.5 | −4.5 | 4.5 | 10.8 | 13.6 |
| SD | 2.2 | 1.3 | 1.2 | 1.8 | 3.2 | 3.1 |
| Mean latency (ms) | 269 | 263 | 305 | 329 | 380 | 410 |
| Stimulus Condition 3 | | | *Subject JB* | | | |
| Mean amplitude (deg) | −15.4 | −8.4 | −3.2 | 3.2 | 7.5 | 11.6 |
| SD | 1.8 | 2.4 | 0.9 | 1.4 | 1.9 | 4.3 |
| Mean latency (ms) | 330 | 335 | 343 | 331 | 362 | 359 |

condition leads to some trials when the stimulus failed to trigger the saccadic system (e.g., for G.: 18% at 10°, 2% at −10°, 30% at 15° and 0% at −15° eccentricity), although when saccades occurred, they were generally accurate. Some presentations using Stimulus Condition 3 also failed to trigger saccades in normal subjects, particularly for the 15° eccentricity (e.g., for J.B.: 6.3% at 10°, 3.3% at −10°, 6.6% at 15°, and 0% at −15°).

*Experiment 2*

Six stimuli consisting of either single or double targets were used in this experiment. Single discs were presented at 5° and 10° on each side of fixation and stimuli consisting of the disc targets (of 5° and 10° eccentricity) were presented either to the left or the right hemifield. The three conditions for stimulus presentation were the same as those used in Experiment 1.

*Single targets.* The results show that the latency and the amplitude values obtained with single targets are consistent with Experiment 1 and that G. responds well to flashed targets. This observation is not unexpected since other experiments have shown that G. is relatively sensitive when presented with either flashed or fast moving targets (Barbur *et al.*, 1980).

*Double targets.* As described in the Introduction, the global effect is shown when saccades to the target pair overshoot the end point of saccades to a single target in the nearest position. A quantification of the effect produced by the second target may be made as follows:

$$\text{GEP} = 100 \times \frac{(\text{double target amplitude-near target amplitude})}{(\text{far target amplitude-near target amplitude})}$$

This measure (Global Effect Parameter, GEP) gives 0% if the distant target has no effect on the saccade and 50% when the double target saccades land at the midpoint of the two single target saccades. The results are summarized in Table 2 and they show a mean global effect parameter of $27 \pm 4\%$. This figure is close to that obtained under similar stimulus conditions in Experiment 2 of Findlay's (1982) paper. The 'global effect' shows some dependence upon saccade latency, being larger for short-latency saccades. The task employed in the present experiment may not have been optimal in this respect, since no emphasis was placed on fast responses;

The results of G.'s saccades to double targets in the blind hemifield do not show a consistent overshoot (Stimulus Condition 1: +28%, Stimulus Condition 2: −13%, Stimulus Condition 3: +2%), although the result from Stimulus Condition 1 suggests that some effect may be present with saccades of short latencies.

In the *normal* hemifield, responses to double targets actually undershoot those to the near target observed in Stimulus Condition 1 and 2 (GEP values of −18% and −8%, respectively). In Stimulus Condition 3, double target responses were found to be extremely variable.

*Experiment 3*

In this experiment identical disc stimuli were presented simultaneously on each side of fixation at an eccentricity of 10°. Single targets at the same eccentricity and blank trials were also included in the sequence. Stimulus Condition 2 was used throughout this experiment.

*Single target and blank trials.* The results are shown in fig. 5A, B for 2 subjects.

TABLE 2 RESULTS OF EYE-MOVEMENT MEASUREMENTS FOR SINGLE AND DOUBLE STIMULI* THE TABLE SUMMARISES THE MEAN AMPLITUDE AND LATENCY VALUES AND THE GLOBAL EFFECT PARAMETER (GEP)

| Eccentricity (deg) | −10 and −5 | −10 | −5 | 5 | 10 | 10 and 5 |
|---|---|---|---|---|---|---|
| Stimulus Condition 1 | | | *Subject G* | | | |
| Mean amplitude (deg) | −4.2 | −10.8 | −5.2 | 5.9 | 8.7 | 6.7 |
| SD | 0.8 | 1.1 | 0.9 | 1.7 | 2.0 | 1.7 |
| Mean latency (ms) | 206 | 175 | 193 | 191 | 167 | 180 |
| GEP | 17.9 | | | | | 28.6 |
| Stimulus Condition 1 | | | *Subject P F* | | | |
| Mean amplitude (deg) | −7.8 | −12.4 | −7.0 | 5.1 | 10.8 | 5.1 |
| SD | 1.2 | 1.3 | 1.2 | 1.2 | 0.7 | 0.9 |
| Mean latency (ms) | 178 | 179 | 185 | 223 | 221 | 211 |
| GEP | 14.8 | | | | | 0.0 |
| Stimulus Condition 2 | | | *Subject G* | | | |
| Mean amplitude (deg) | −4.3 | −11.2 | −4.8 | 5.9 | 8.8 | 5.4 |
| SD | 0.8 | 1.1 | 0.7 | 1.7 | 1.6 | 1.4 |
| Mean latency (ms) | 194 | 186 | 189 | 212 | 229 | 206 |
| GEP | −7.8 | | | | | −17.2 |
| Stimulus Condition 2 | | | *Subject J B* | | | |
| Mean amplitude (deg) | −7.1 | −11.2 | −5.4 | 4.4 | 9.6 | 5.6 |
| SD | 1.3 | 0.6 | 0.6 | 1.2 | 2.2 | 0.9 |
| Mean latency (ms) | 239 | 279 | 275 | 250 | 276 | 217 |
| GEP | 29.3 | | | | | 23.1 |
| Stimulus Condition 3 | | | *Subject G* | | | |
| Mean amplitude (deg) | −7.5 | −9.9 | −4.5 | 5.2 | 9.3 | 5.3 |
| SD | 4.7 | 1.3 | 1.5 | 1.6 | 2.1 | 2.2 |
| Mean latency (ms) | 311 | 264 | 322 | 286 | 324 | 359 |
| GEP | 55.6 | | | | | 2.4 |
| Stimulus Condition 3 | | | *Subject J B* | | | |
| Mean amplitude (deg) | −6.5 | −9.5 | −5.0 | 4.2 | 10.0 | 5.7 |
| SD | 1.1 | 1.6 | 1.6 | 1.2 | 2.2 | 0.9 |
| Mean latency (ms) | 208 | 325 | 258 | 252 | 279 | 252 |
| GEP | 33.3 | | | | | 25.9 |

* The visual stimulus was either a single, 2° diameter disc, or two identical discs presented either at +10° and +5°, or at −5° and −10° eccentricity GEP = Global Effect Parameter

Both subjects show an extremely small number of saccades to blank trials (i.e., 4% for G., and 8.5% for J.B.). This observation indicates that G. is not adopting a strategy of making a search saccade whenever no stimulus appears in the seeing hemifield.

*Bilateral trials.* When presented with bilateral stimuli, normal subjects show increased latencies (Lévy-Schoen, 1969; Findlay, 1983). G. saccades exclusively to the target presented in his seeing hemifield, although on some 6% of these bilateral trails he fails to saccade at all and maintains foveal fixation. In contrast, a single stimulus at 10° in the normal hemifield always elicits a correct saccade (*see* fig. 5A). His responses to bilateral targets show no significant difference in either latency or amplitude when compared with unilateral targets. During this experiment G. reported that he was also 'aware' of the target in his blind hemifield when he was presented with a bilateral stimulus. His immediate response, however, was to

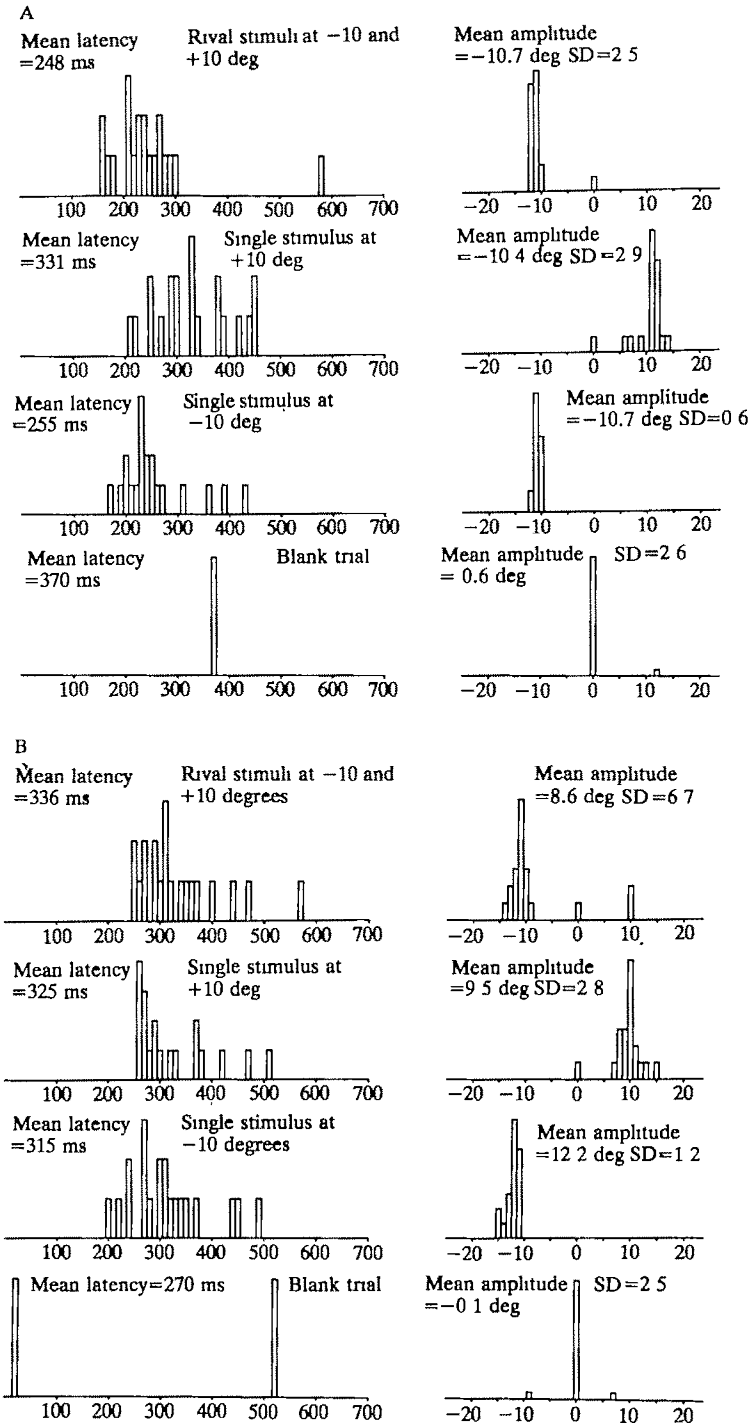


FIG. 5 Eye-movement frequency response histograms for single and rival stimuli and for blank trials. The stimuli were presented using Stimulus Condition 2. A, Subject G., B, Subject J.B.

saccade towards the stimulus in his normal hemifield. Data for the normal subject, J.B. show increased latencies in bilateral trials and a tendency to saccade towards the stimulus in the left hemifield (i.e., 10% to 10°; 84% to −10° and 6% with no response). Similar experiments with the left field stimulus reduced in luminance by 1 log unit have been performed with J.B. and the results were very similar to those shown in fig. 5B. These findings suggest that the dominance of the —10° bilateral stimulus in triggering the saccadic system is not due to a difference in sensitivity between the two parts of the visual field.

### *Experiment 4*

This experiment employed a series of single 1° diameter targets presented at an eccentricity of 5°, 10° and 15° on either side of fixation, together with blank trials. Two luminance series were used for targets imaged in G.'s blind hemifield and in each series the luminance of the target was adjusted so as to produce an equal amount of scattered light over the foveal region for each target position. The results obtained and the luminance values used are shown in Table 3 for each eccentricity. Similar experiments were also carried out with different background luminance

TABLE 3. SUMMARY OF SACCADIC EYE-MOVEMENT PARAMETERS FOR DIFFERENT TEST AND BACKGROUND FIELD LUMINANCE LEVELS AND DIFFERENT STIMULUS ECCENTRICITIES. SUBJECT G., STIMULUS CONDITION 2: 1° STIMULUS DIAMETER

| Eccentricity (deg) | −15 | −10 | −5 | 5 | 5 | 10 | 10 | 15 | 15 |
|---|---|---|---|---|---|---|---|---|---|
| Test stimulus Increment Luminance (cd/m²) | 79 | 26.2 | 7.4 | 12.2 | 7.4 | 41.5 | 26.2 | 123 | 79 |
| Background luminance = 20.3 cd/m² | | | | | | | | | |
| Latency (ms) | 314 | 285 | 287 | 482 | 569 | 491 | 511 | 558 | 535 |
| SD | 51 | 46 | 34 | 59 | 95 | 81 | 94 | 73 | 75 |
| Amplitude (deg) | −13.8 | −9.8 | −5.5 | 7.4 | 8.4 | 9.9 | 9.4 | 9.7 | 10.3 |
| SD | 0.9 | 0.6 | 1.2 | 1.6 | 1.9 | 1.2 | 0.9 | 2.0 | 1.4 |
| Background luminance = 11.5 cd/m² | | | | | | | | | |
| Latency (ms) | 283 | 259 | 258 | 485 | 525 | 487 | 483 | 575 | 690 |
| SD | 15 | 17 | 12 | 97 | 139 | 103 | 106 | 115 | 0 |
| Amplitude (deg) | −13.6 | −10.0 | −5.2 | 6.2 | 8.2 | 10.2 | 9.6 | 8.0 | 10.0 |
| SD | 0.7 | 0.4 | 0.4 | 1.3 | 0.8 | 1.6 | 1.4 | 2.0 | 0 |
| Background luminance = 5.3 cd/m² | | | | | | | | | |
| Latency (ns) | 288 | 258 | 255 | 384 | 417 | 400 | 416 | 581 | 561 |
| SD | 34 | 28 | 21 | 67 | 104 | 67 | 77 | 115 | 123 |
| Amplitude (deg) | −13.9 | −9.5 | −5.0 | 5.5 | 6.3 | 9.3 | 9.3 | 10.6 | 11.3 |
| SD | 0.7 | 0.5 | 0.3 | 0.9 | 1.5 | 0.9 | 1.1 | 0.7 | 2.1 |
| Background luminance = 1.5 cd/m² | | | | | | | | | |
| Latency (ms) | 254 | 236 | 266 | 286 | 317 | 309 | 320 | 392 | 391 |
| SD | 39 | 20 | 53 | 35 | 85 | 75 | 100 | 149 | 160 |
| Amplitude (deg) | −14.3 | −9.9 | −5.2 | 5.0 | 5.1 | 9.4 | 9.2 | 11.4 | 10.5 |
| SD | 0.9 | 0.5 | 0.4 | 0.7 | 0.6 | 1.3 | 1.3 | 2.0 | 1.8 |
| Background luminance = 1.5 to 11.2, excluding latencies > 350 ms | | | | | | | | | |
| Latency (ms) | 273 | 253 | 254 | 293 | 296 | 286 | 289 | 278 | 285 |
| SD | 31 | 25 | 19 | 35 | 39 | 40 | 37 | 32 | 40 |
| Amplitude (deg) | −14.0 | −9.7 | −5.1 | 5.0 | 5.2 | 8.9 | 8.9 | 10.1 | 10.3 |
| SD | 0.8 | 0.5 | 0.4 | 0.7 | 0.7 | 0.8 | 1.1 | 1.7 | 1.8 |

levels so as to be able to assess the effect of target contrast on the probability of a correct saccadic response.

The results provide a clear demonstration of accurate saccades to 5° and 10° targets when presented in the blind hemifield. The 15° targets, however, seem to produce saccades which always fall short, but are significantly larger than those for 10°. At high contrast levels, no consistent latency differences are observed between 5° and 10° targets or for the two test target luminance levels used at each eccentricity.

*Effect of stimulus contrast.* The results show that correct saccadic eye movements can be elicited with the stimulus presented in the blind hemifield even when the luminance of the test stimulus is adjusted so as to yield the same amount of scattered light over the foveal region for all eccentricities. If the contrast of the stimulus is below the threshold level required at a given eccentricity, no saccadic eye movement is generated, although with the stimulus close to threshold level, a very long-latency saccade can sometimes be observed. The use of many trials for each test target/background field combination can provide a way of calculating the probability of a correct saccadic response when the stimulus is presented to G.'s blind hemifield. A detailed analysis of G.'s responses was undertaken and the percentage number of correct saccades which had a latency of less than 350 ms was calculated for each ratio of stimulus to background field luminance used in the experiment. Probit analysis of these psychometric functions which relate the probability of a correct saccade to log $(L_t/L_b)$ values was used to extract the test target to background luminance ratio necessary to give 50% probability of saccade occurrence (Finney, 1971). The results are shown in fig. 6 and they reveal a systematic increase in threshold values with stimulus eccentricity. The calculated log $(L_t/L_b)$ values for 50% probability of saccade occurrence for stimuli presented at 5°, 10° and 15° eccentricity were 0.21, .87 and 2.12 log units, respectively.

*Subjective reports by Subject G.* In all experiments G. reported that he was not able to 'see' any visual stimulus when these were presented in his blind hemifield. In spite of this lack of normal visual sensation, G. reported on many occasions that he was 'aware' of the stimulus although he could not 'see' it. When G. was presented with a flash stimulus of progressively higher luminance level his description of the stimulus can be summarized as follows. At low light levels he failed to detect or to be aware of anything in his blind hemifield. His eye movement responses were less accurate and of much longer latency. Such stimuli generally failed to trigger short-latency saccades, but G.'s eye movements were always directed towards the stimulated area of the blind hemifield. His responses were therefore different to those observed in the absence of any stimulus, (i.e., blank trials) when G. did not saccade at all. As the luminance level of the stimulus was increased, he reported that he was aware of the stimulus and its spatial location although he could not see it. At very high light levels, he admitted to some form of seeing which he described as a change in the level of darkness at the corresponding location in the blind hemifield. Under these conditions, G.'s saccadic eye movements were also accurate and of short latency. When presented with bilateral stimuli (*see* Experiment 3), he reported that he was 'aware' of the stimulus presented to his blind hemifield, but that he always found it easier to saccade towards the stimulus in the normal hemifield.

## DISCUSSION

### *Scattered light*

The role of nongeniculostriate projections in human vision is not entirely understood and therefore the unusual nature of 'blindsight' or the existence of residual visual functions in 'blind' areas of the visual field, as in lesions of the striate cortex, has often been questioned (*see* Campion *et al.*, 1983). In order to guard against possible artefactual results, particular care must be exercized so as to ensure that the subject does not detect the stimulus or stimulus-related information via other sensory modalities or via the unaffected areas of the visual field.

G.'s visual performance was thoroughly investigated in previous studies (Barbur *et al.*, 1980; Grounds *et al.*, 1983), which show that for G.'s blind field, residual vision cannot be explained in terms of scattered light or other stimulus artefacts. The present study involved a different test of visual performance using different stimulus conditions and therefore the possibility of scattered light was again very carefully examined. All experiments employed a large uniform background field of width 100° and height 40°. The stimulus was always presented at a randomly selected eccentricity and the subject's fixation before the presentation of the stimulus was carefully monitored. Stimulus Condition 3 was used to ensure that the offset of the trigger stimulus preceded the onset of a normal saccade. This condition therefore eliminates the possibility of stimulus detection following an initial search saccade. Although G.'s performance following blind field stimulation is comparable to that observed in his normal hemifield under all stimulus conditions, the possibility remains that G. bases his responses on the amount of scattered light which is known to depend on stimulus retinal illuminance, stimulus shape and size and the visual angle between the stimulus 'source' and the area of interest on the retina. For small circular glare sources the effect of scattered light is found to decrease as $1/\theta^n$, with typical n values in the range 1.5 to 2 (*see* review by Wyszecki and Stiles, 1982).

Experiment 4 was designed to circumvent the light scatter argument by using a disc stimulus of 1° diameter (i.e., constant shape and size), whose retinal illuminance and presentation eccentricity were randomized. For each stimulus eccentricity, two test target and four background luminance levels were used. The luminance of the test target was adjusted so as to yield approximately the same amount of scatter over the foveal region, irrespective of target location. This was achieved by making the luminance of the target proportional to the square of its eccentricity. The various combinations of test and background luminance levels used in this experiment are summarized in Table 3. Under these stimulus conditions the subject can no longer

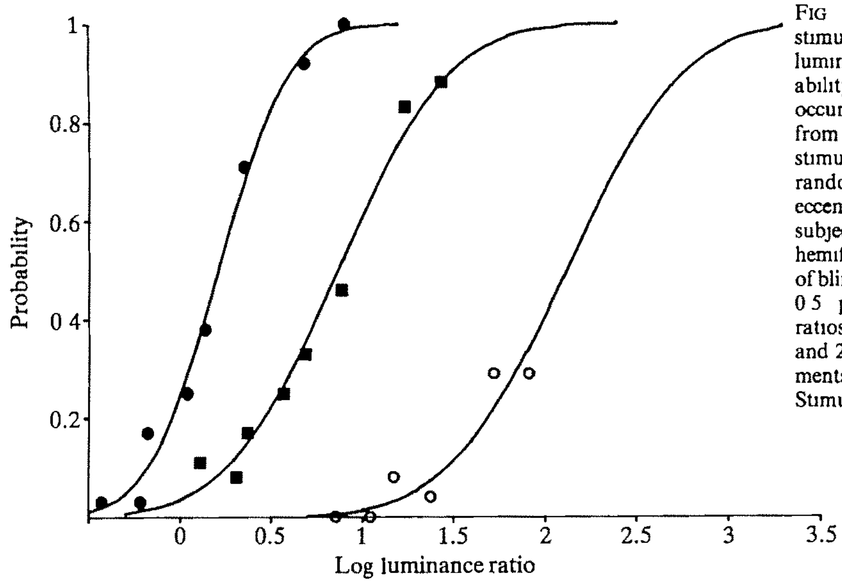


FIG. 6. The effect of test stimulus to background field luminance ratio on the probability of correct saccade occurrence within 350 ms from stimulus onset. The stimuli were presented at randomly selected, discrete eccentricity values in the subject's normal and blind hemifields. Probit analysis of blind hemifield data yields 0.5 probability luminance ratios of 0.21 (5°), 0.87 (10°) and 2.12 (15°). All measurements were carried out using Stimulus Condition 2.

make use of the amount of scatter as an indication of stimulus eccentricity. In spite of these stimulus conditions, G. was able to make appropriate saccades to 5° and 10° target locations in either hemifield. The results (*see* Table 3) show that blind field stimulation produces saccades of accurate mean amplitude irrespective of stimulus luminance, provided that the contrast of the stimulus is above the threshold level for saccade generation at a given eccentricity. Fig. 6 shows how the contrast threshold for saccade generation increases with stimulus eccentricity. The 50% contrast threshold level is particularly large when the stimulus is presented 15° in the periphery and this may be partly due to decreased sensitivity when the stimulus is presented in the vicinity of the blind spot region. Short latencies of less than 350 ms and relatively accurate saccades were recorded for target contrast values which were above threshold level. Moreover, since under photopic condition of illumination the foveal region possesses the highest sensitivity (*see* spatial map of retinal sensitivity for G. in Barbur *et al.*, 1980), it is expected that under conditions of equal foveal scatter, the subject would always saccade to the same eccentricity. The experimental results immediately rule out the possibility that the hemianope generated saccades whose amplitudes were an inverse function of light scatter. The possibility remains that the pattern, rather than simply the amount of scatter into the normal hemifield, was sufficient to provide G.'s saccadic eye movement system with information about the position of the target. Since the stimulus shape and size which can affect the pattern of light scatter remained unchanged throughout each experiment, this explanation is extremely unlikely. The experimental results also provide evidence against this possibility. The analysis of changes in the complex pattern of scattered light necessitates a longer processing time and therefore if this were the case, much longer saccade latencies would be expected. The results show that stimulation in G.'s blind hemifield can trigger the generation of rapid and accurate saccades which for some stimulus conditions have the same mean latency as those observed in the normal hemifield (*see* Tables 1, 2, Stimulus Condition 1). It is therefore concluded that neither the pattern nor the amount of light scatter under the stimulus conditions of this investigation can be used to explain G.'s ability to saccade towards targets presented to his blind hemifield.

### *Other studies*

Many investigations of residual vision in subjects with scotomas associated with cortical lesions or damaged geniculostriate pathways, have examined the patient's ability to localize visual stimuli when presented to the blind areas of the visual field. Some tests of spatial localization were based on the measurement of saccadic eye movements (Pöppel *et al.*, 1973; Weiskrantz *et al.*, 1974; Zihl and von Cramon, 1980; Zihl, 1981). These studies investigate mostly the 10° to 40° region of the visual field (partly because of the restrictions of the EOG technique). As pointed out by Weiskrantz *et al.* (1974), there are reasons for supposing that for the purposes of saccade generation, two regions of visual space should be distinguished with a boundary at about 15° eccentricity. For eccentricities below 15°, target localization is frequently achieved by an eye movement alone; above 15° a head movement also occurs when the head is free to move (Gresty, 1974). In experimental studies (summarized in Findlay, 1983), no systematic dependence of saccade latency on target eccentricity occurs below 15°, whereas for higher values increasing latencies are found as target eccentricity increases. Saccades to targets at eccentricities greater than 15° are always made in two stages, the first saccades showing a systematic undershoot followed by a smaller corrective movement (Frost and Pöppel, 1976). On the basis of their observations, Frost and Pöppel suggest the existence of two programming modes for the generation of saccadic eye movements below and above 15°, respectively.

This possibility might go some way towards explaining why previous workers have not always been successful in demonstrating visually-guided saccades when the stimulus was presented in scotomas outside the central 30° of the visual field. Acquisition of a target above 15° eccentricity with a saccadic eye movement alone is not the normal response mode. The generation of secondary corrective saccades following blind field stimulation at large eccentricities may not always be possible since the results of other experiments show that G. is not aware of stationary targets in his blind hemifield and that he can only respond to either flashed or fast moving targets (Barbur *et al.*, 1980). Following the first saccade which can be triggered by the onset of the test flash, the subject is no longer aware of the position of the target and therefore in the absence of position information he would have to make use of less accurate search saccades. In normal vision this is not the case, since information regarding the location of the target following the first saccade is available to the subject and therefore it can be used in determining the parameters of the corrective saccade.

Other important factors which can significantly affect the observed responses concern the extent and the location of the damage which causes the loss of normal vision in discrete areas of the visual field, the subject's age when the damage occurs and the recovery period following the accident. Differences in eye movement performance and the degree of variability observed for different subjects is therefore not entirely unexpected. The subject of our investigation had a car accident when 8 years old which resulted in localized damage to his left cerebral hemisphere. The long recovery period and the early age of his accident may account for his ability to localize briefly presented or fast-moving targets in his blind hemifield, either by means of eye movements or verbal responses (Barbur *et al.*, 1980).

### *Normal saccadic eye movements (accuracy and variability)*

The properties of saccades generated by means of visual stimuli have been studied extensively in normal subjects (Carpenter, 1977; Findlay, 1983). Acquisition of a target presented visually in the range 1° to 10° is normally achieved with a single saccade. Systematic variations from the target position are rarely more than 0.5° and variability, measured as the SD of saccade amplitudes to a particular target, increases from about 0.2° for targets at 2° eccentricity to 0.6° to targets at 10° eccentricity. For targets at larger eccentricities, the first saccade shows a systematic undershoot, typically 10% of the target eccentricity, and is usually followed after a short latency by a further corrective saccade. The short latency indicates that these corrective saccades are centrally planned.

The pattern shown by G. in his normal hemifield is consistent with these findings. In his blind hemifield, saccade amplitudes to 5° and 10° targets are normal, but those to 15° targets show a much larger undershoot than normal, which brings them close to the size of saccades to 10° targets. The results in fig. 5 suggest that the contrast of the target when presented 15° in the blind hemifield was not always above threshold level. The latencies were also larger, and larger SDs were observed for both latency and amplitude measurements. Another interesting observation emerges from the analysis of first corrective saccades as measured for the 15° target. The results show a mean response latency of 244 ms for the normal hemifield as opposed to 165 ms for the blind hemifield. The mean amplitude following the first corrective saccade was 15.1° for the normal hemifield, but only 13.4° for the blind hemifield. These data were extracted from the results of Experiment 1 using Stimulus Condition 1 and they suggest that the relatively short-latency corrective saccades in the blind hemifield lacked target position information and were therefore similar to search saccades. In the normal hemifield the first corrective saccades had a longer latency and showed greater accuracy. These observations suggest that G. was not able to extract the position of the stationary stimulus following the first saccade. The pattern of eye movement responses in G.'s blind hemifield for target eccentricities which would normally require corrective saccades may therefore be different to that observed in normal vision.

### *Temporal properties of saccades*

It is generally believed that the generation of a saccade requires a temporal trigger signal (activation of the 'WHEN' system). For a saccade to a visual target, it is possible for this signal to arise from the target itself, but also the system may be primed by signals from other sources, such as warning signals. The evidence for this is that large decreases of latency are possible with suitable warning signals in the 'absence' of any information from the visual target (*see* Findlay, 1983; 1985).

The results obtained in G. are consistent with this scheme. In the normal hemifield, latencies are practically independent of stimulus intensity and contrast (*see* Table 3), showing a small increase in latency at 15° eccentricity above that for 5° and 10°. For Stimulus Condition 1 in Experiments 1 and 2, there is little difference between blind and normal hemifield presentations. This is the condition in which the fixation point offset acted as a warning signal and the target had high temporal predictability. In other conditions, the information associated with the appearance of the target was more important in the saccade initiation process. Whereas in the normal hemifield the characteristics of the target had little effect on latency in all experiments, in the blind hemifield the latencies now seem systematically related to the effective contrast of the target. This may be due to the higher contrast thresholds required for saccade generation and the increase in threshold with eccentricity (*see* fig. 6). Whereas in the normal hemifield the stimulus was always well above contrast threshold level, this was not always the case in the blind hemifield, particularly in Experiment 4 which employed a smaller size target and a range of test target and background field luminance levels. Previous studies with G. have shown that his blind hemifield has different spatial and temporal properties from those observed in normal vision. The blind hemifield exhibits large spatial summation, a relatively high sensitivity for detection of transient events such as fast movement or target onset and offset and poor sensitivity for detection of repetitive events. In line with these findings the threshold contrast level for saccade generation shows similar dependence on target size, eccentricity and mode of presentation. Fig. 5 shows that short latency, accurate saccades into the blind hemifield require higher stimulus contrast levels by comparison with the normal hemifield. With the target contrast close to threshold level the subject either fails to make any eye movements or his saccades are inaccurate and of long latency.

### *Double targets*

The expectation that G. would show a consistent global effect with double targets was not fulfilled. Indeed with one exception, saccades to double targets in the blind hemifield show no effect of the more distant target (*see* Table 2). The exception is in Experiment 2, Stimulus Condition 1, and is of some interest because this condition produces saccades with latencies of around 180 ms. In all other double target conditions, saccade latencies were longer, often considerably so. It is found with normal subjects that the influence of the second target is greater when the saccade latency is small and thus G.'s double target saccades in the blind hemifield are no different from those which might be expected from a normal subject making a saccade with the same latency. Clearly the hypothesis that the global effect is an inevitable outcome of midbrain processing can be rejected.

G.'s saccades to double targets in his normal hemifield did show an interesting result, however. These saccades are of smaller amplitude than those to the single near target. This effect is small but consistent. It appears that the presence of a second target has the opposite effect to that found in normal subjects. Functionally, an explanation is readily apparent. If G. produced a normal global effect to target pairs in the normal hemifield, his gaze would move to an intermediate position between the targets and thus the rightmost target would fall in his blind hemifield. Such a saccade would be maladaptive since it would result in loss of visibility of the target.

How does this finding of undershoot to target pairs relate to the finding of overshoot in normal subjects? The extent of global effect overshoot can be modified by voluntary influences in normal subjects. Findlay and Crawford (1983) have shown that practice over a period of one week in a situation requiring very precise fixation led to reduction of the overshoot from 30% to around 10%. Although it appeared that a steady asymptote had been reached, the time scale is very much shorter than that available for G. It has been suggested that global processing of target pairs represents a default option for normal vision (Ottes *et al.*, 1984). This form of processing may confer advantages in processing speed (J. M. Findlay and T. J. Harris, unpublished observations), and thus be used unless concomitant disadvantages arise as would be the case in hemianopic patients. The finding of a reversed effect suggests that a form of spatial processing is being used which extracts the field position of the nearest feature in the target. These observations suggest that G. has developed a strategic response pattern which maximizes the use of his normal hemifield. Similar results have been found in previous investigations (Meienberg *et al.*, 1981). In the double stimulus experiment, we do not, however, find significant overshoot with respect to the nearest target when the double stimulus was presented at 5° and 10° eccentricity, except in Experiment 1, Stimulus Condition 1, which also produced short latency saccades. Random search saccades have been observed in some cases when the stimulus contrast was close to threshold level. This was often observed in Experiment 4 with the stimulus presented at an eccentricity of 15°. This experiment employed a smaller diameter target and therefore the stimulus contrast was often below threshold level. Another interesting observation concerns the pattern of saccadic eye movements when the hemianope was presented with a large, uniform background field and asked to attend to any stimuli presented in the field. Recordings taken over a period of 2 min using an infrared video camera show that in the absence of a stimulus the number of large, search saccades into the blind hemifield is much larger than that observed in the seeing hemifield. This presumably unconscious response pattern is of advantage to the hemianope since it compensates for the decreased sensitivity of the blind hemifield as compared with the normal hemifield.

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# THE CHARACTERIZATION OF EXPERIMENTAL GLIOSIS BY QUANTITATIVE NUCLEAR MAGNETIC RESONANCE IMAGING

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## SUMMARY

Quantitative nuclear magnetic resonance imaging techniques were used to study the development of astrocytic gliosis following a cortical freezing injury in 4 cats, and the findings compared with the histological and ultrastructural appearances of the affected white matter. In the first week after lesioning, the acutely oedematous white matter was apparent as a region of signal abnormality with very prolonged $T_1'$ and $T_2'$ relaxation times. Following resolution of this oedema, the images remained normal for a period of approximately three months. After this latent period they became abnormal once again, and the abnormal signal was most evident in images emphasizing differences between tissues in $T_1'$ and proton density, but not $T_2'$. The light and electron microscopic appearances of the corresponding tissue were of astrocytic gliosis in each animal. Measurement of the relaxation times, $T_1'$ and $T_2'$, of the abnormal regions revealed an increase in $T_1'$ without a corresponding change in $T_2'$. The $T_2'$ magnetization decay characteristics were consistently monoexponential, in contrast to the clearly biexponential $T_2$ decay which has previously been demonstrated in the presence of acute vasogenic oedema. These findings suggest that the pattern of change of the relaxation times and $T_2$ magnetization decay might provide a means of distinguishing between lesions in multiple sclerosis which are predominantly gliotic, and those containing significant amounts of oedema.

## INTRODUCTION

Astrocytic gliosis follows many types of damage to the central nervous system (CNS), including that caused by multiple sclerosis (MS) (Duchen, 1984). A typical glial scar appears macroscopically as a yellow-grey, contracted region. When examined microscopically, the appearances are of 'octopus-like astrocytes holding the manifold structures of the nervous system within their tentacles' (Penfield, 1927). Progressive and extensive proliferation of astrocyte processes results ultimately in a network which replaces, to a greater or lesser extent, the normal cerebral structures. These processes contain numerous bundles of glial fibrils which characteristically stain for glial fibrillary acidic protein (Bignami *et al.*, 1972); the cell type

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responsible for this reaction has a fibroblast-like morphology (Raff *et al.*, 1983) and has been classified as the type 1 astrocyte (Miller *et al.*, 1986).

The distribution of deep white matter MS lesions corresponds closely with that of the regions of abnormal signal in nuclear magnetic resonance (NMR) images (Ormerod *et al.*, 1986, 1987; W. A. Stewart, L. D. Hall, K. Berry, personal communication, 1986). Since gliosis is an important pathological feature of these lesions (Adams, 1977), the possibility arises that this process may, at least in part, be responsible for the abnormal magnetic resonance imaging (MRI) appearances of the brain in this disease (McDonald, 1986).

We have previously reported the quantitative MRI findings of a study of acute vasogenic oedema induced in cats by cortical freezing (Barnes *et al.*, 1987). Over a period of months following this injury, progressive gliosis develops extensively in white matter which has been rendered oedematous in this way (Long *et al.*, 1973). We have therefore carried out a serial study of the cold lesion by quantitative MRI and terminal electron microscopy.

## METHODS

Four adult cats were used in this study. Following a control MRI examination, a cold lesion was produced over the right middle suprasylvian gyrus of each animal as described previously (Barnes *et al.*, 1987). Following resolution of the acute oedema approximately 1 week after lesioning, the animals were studied sequentially by MRI until sacrifice at intervals after lesioning of 7 months in 1, 6 months in a second, and 5.5 months in the remaining 2. The experiments described in this study were carried out over a total period of 8 months.

### *NMR imaging*

Full details of the MRI experimental techniques and methods of relaxation time measurement are described in the Appendix. The imaging studies were performed on a Picker International system operating at 0 5 Tesla. Image pixel dimensions were 0.6 × 0.6 × 5 mm The animals were examined at intervals of 2–4 weeks during the experimental period. Prior to imaging, each animal was anaesthetized by an intraperitoneal injection of pentobarbitone (Sagatal; May and Baker) in a dose of 40 mg/kg. Following localization of the cortical lesion with coronal and sagittal pilot scans, a series of single slice inversion recovery (IR) and spin echo (SE) images were acquired in the coronal plane at the level of the cortical lesion

The relaxation times, $T_1$ and $T_2$, were read directly from calculated images, each generated from a pair of conventional images. As this two-point method of calculation assumes a monoexponential relaxation process which may not apply in biological systems, the values obtained may be approximations, and are therefore denoted $T_1'$ and $T_2'$.

The $T_2$ magnetization decay (MD) curves were derived from the regions of abnormal white matter signal in the 4 experimental animals by reading the signal intensity of the region of interest from the SE images. An iterative computed least-squares fitting procedure was then applied to the data; best fits were sought for mono- and biexponential $T_2$ decay functions In the present experiments, $T_1$ relaxation was assumed to be monoexponential: where biexponential $T_1$ relaxation has been observed in biological tissues by in vitro NMR, one component has relaxed too rapidly to be detectable by our technique (Edzes and Samulski, 1978, Bakker and Vriend, 1984).

### *Histology and ultrastructure*

Each animal was killed after the final imaging session by transcardiac, intra-aortic perfusion-fixation with 3% glutaraldehyde in cacodylate buffer (pH = 7.4). After a further 48 h in fixative, the brains were removed and a series of 3 mm thick coronal sections were taken, centred on the circular cortical scar Tissue samples were postfixed in 1% osmium tetroxide, dehydrated in graded ethanol solutions, and embedded in epoxy resin. Semithin sections (0.5 μm) were stained with toluidine blue for light microscopy, and ultrathin sections (60 nm) with methanolic uranyl acetate and Reynold's lead citrate for examination by transmission electron microscopy.

## RESULTS

The animals showed no clinical abnormalities at any time during the experimental period.

### *Macroscopic appearances*

The site of application of the cold probe was visible on the surface of the brain as either a yellow circular scar or, in one animal, as a small cavity indenting the cortex of the suprasylvian gyrus. The cut brain surfaces showed only minor abnormalities; the white matter of the lesioned gyrus, and that of the adjacent callosal radiation and lateral gyrus, showed a greyish discolouration. Apart from the localized cortical scar, grey matter structures and white matter more distant from the lesion appeared normal.

### *Microscopic appearances*

The most marked pathological changes were found in tissue samples from the regions which had appeared macroscopically discoloured, and extended for 6 to 9 mm in an anteroposterior direction.

By light microscopy, the affected tissue appeared hypercellular, containing numerous large cell bodies whose nuclei often displayed dispersed chromatin (fig. 1). The most striking feature was diffuse separation of the normal tissue elements by sheets of poorly stained material which were sometimes seen to be in continuity with the large cell bodies. Nerve fibres and their associated myelin sheaths were of normal appearance. Ultrastructurally, the anatomical extent of the pathological changes corresponded closely with that seen by light microscopy. In the most abnormal samples, astrocytic processes filled with densely packed glial fibrils occupied most of the tissue (fig. 2). Consequently, the visible nerve fibres and oligodendrocyte processes were considerably reduced in number compared with normal white matter. Specialized junctional complexes of varying morphology were often seen where astrocyte processes lay adjacent to each other, and no enlargement of the extracellular space was apparent. White matter more distant from the cortical lesion showed similar, but milder changes.

In general, the severity of the gliotic process in each animal was related to the

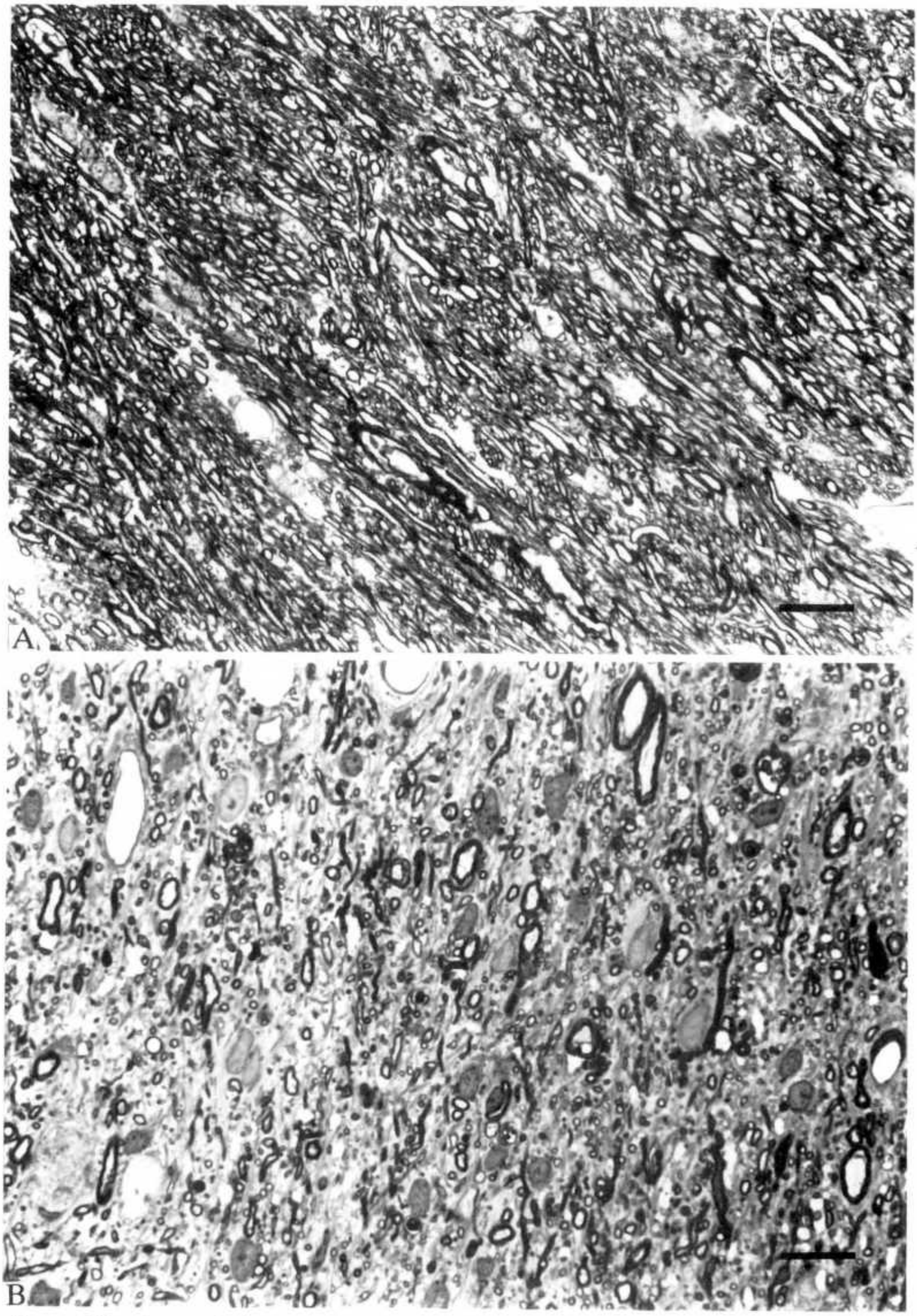

FIG. 1. Light micrographs showing (A) normal and (B) gliotic white matter. The gliotic tissue shows separation of normally myelinated nerve fibres by sheets of glial fibrils, and an increased number of astrocyte nuclei. Toluidine blue. Bars = 20 $\mu$m.

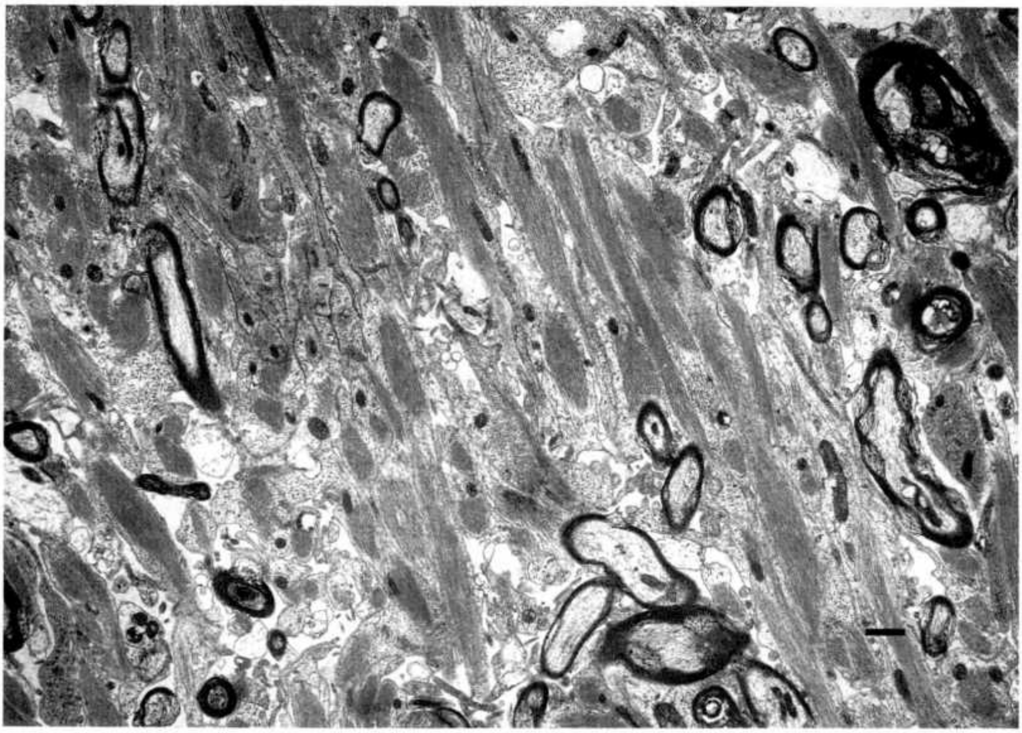

FIG. 2. Electron micrograph of gliotic white matter showing abundant astrocyte processes containing densely packed glial fibrils. The widely separated nerve fibres appear normal. Bar = 1 μm.

duration of its development; it was most severe in the 7-month animal, and only moderate in the animals sacrificed 5.5 months after lesioning.

### *MRI findings*

Following resolution of the acute oedema (fig. 3) after 7 to 10 days, the MRI appearances of the white matter subjacent to the cortical lesion returned to normal. After a latent period of approximately 3 months, mild changes in signal intensity became apparent in the suprasylvian and lateral gyri, and the adjacent part of the callosal radiation. Thereafter, this region became progressively more abnormal until the animal was killed, but in no case was its anatomical distribution as extensive as that of the oedema which had been present immediately after lesioning (fig. 4). In each animal, the change in signal intensity was mild and most clearly visible on images emphasizing differences in proton density (i.e., short-$T_E$ SE), and the more $T_1$-weighted IR images. Comparison with the ultrastructural findings revealed that the anatomical extent of the abnormal MR signal corresponded with regions affected by moderate and severe gliosis; where the pathological changes were relatively mild, the signal was normal.

The measured $T_1'$ and $T_2'$ of unaffected tissue in each animal remained stable throughout the experimental period. The $T_1'$ calculated images demonstrated

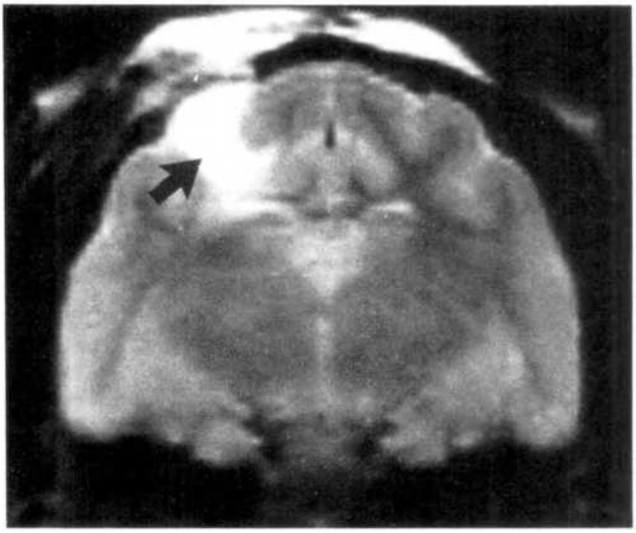

FIG. 3. $T_1$-weighted coronal MR image of cat brain. The region of abnormal signal (arrowed) represents vasogenic oedema at 24 h after cortical freezing. The oedema occupies the right suprasylvian gyrus, spreading into the lateral gyrus and internal capsule. $IR_{2000/200/40}$.

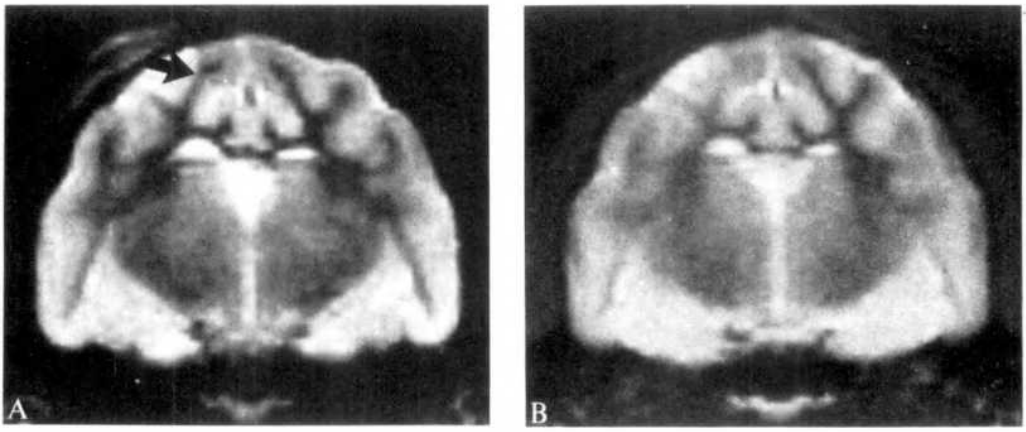

FIG. 4. $T_1$-weighted coronal MR images of the same animal as fig. 3, acquired at (A) 2 months and (B) 7 months after cortical freezing. By 7 months the signal intensity has become abnormal in white matter adjacent to the lesioning artefact. The abnormal signal is most obvious in the lateral gyrus (arrowed). $IR_{2000/200/40}$.

regions of increased relaxation time which corresponded to the abnormal areas of the IR images. By contrast, the $T_2'$ calculated images showed no definite abnormalities. The Table gives the absolute values of $T_1'$ and $T_2'$, and the ratio between them, from control white matter and from the region of abnormal white matter at the final imaging session before killing. In each animal, there was a predominant increase in $T_1'$ of the abnormal white matter which resulted in a corresponding increase in the ratio of $T_1'/T_2'$.

Determination of the $T_2$ MD characteristics may provide further information

TABLE RELAXATION TIMES AND RATIO BETWEEN THEM FOR ABNORMAL TISSUE IN EACH ANIMAL WITH CONTROL VALUES

| *Animal* | $T_1'$(ms) | $T_2'$(ms) | $T_1'/T_2'$ |
|---|---|---|---|
| 1 | 650 | 89 | 7 3 |
| 2 | 565 | 91 | 6 2 |
| 3 | 528 | 85 | 6 2 |
| 4 | 559 | 88 | 6 35 |
| Mean | 575* | 88 | 6 5* |
| Control mean | 483 | 85 | 5 7 |
| Range | (479–487) | (84–86) | (5 6–5 7) |

* significant difference (Mann-Whitney test for nonparametric data, $P < 0\ 05$) between the control and experimental values

about the physical properties of the major tissue compartments, and the rate of exchange of water molecules between them. In each experimental animal, the region of abnormal signal yielded MD data from which a biexponential function could not be derived by the least squares fitting procedure. The monoexponential functions were therefore considered to describe the $T_2$ MD characteristics of these regions most appropriately.

## DISCUSSION

Astrocytic gliosis was successfully induced in each of the experimental animals. The histological and ultrastructural features of gliosis described in these experiments are consistent with those previously reported following cold lesions (Rubinstein *et al.*, 1962; Long *et al.*, 1973) and many other insults to the CNS such as focused ultrasound (Åström *et al.*, 1961). Normal white matter consists predominantly of closely packed nerve fibres, over 90% of which are myelinated (Prineas and Connell, 1978); the extracellular space occupies about 15 to 20% of this tissue (Rees *et al.*, 1982). As a result of gliosis the nerve fibres are largely replaced by numerous astrocyte processes filled with dense bundles of glial fibrils, and bound together by specialized junctional complexes. The anatomical extent of gliosis observed in this study, however, was less than that reported by Long *et al.* (1973) using the same experimental model. This group described the gliosis 'spreading almost as the oedema front had spread'. Nevertheless, the pathological changes observed in the present experiments were uniform within the lesioned gyrus and adjacent white matter to an anteroposterior extent of almost 1 cm.

The changes on the NMR images corresponding to the gliosis found on post-mortem examination, did not appear until about 3 months after the acute oedema had resolved. The existence of this latent period has implications for the assessment of patients by MRI following an acute cerebral insult such as trauma. The development of a symptom such as focal seizures in the first 3 months following the insult may be accompanied by normal image appearances. The results of this study suggest that such a finding cannot be taken as evidence that progressive pathological changes are not occurring. Similarly, it has previously been suggested that some

MS lesions demonstrated by MRI may 'vanish' when reexamined 3 months later (E. Herbe, D. Uhlenbrock, ... personal communication *et al.*, 1986). The finding of a latent period between the acute oedema and chronic gliotic phases of the cold lesion during which the images remain normal suggest that some such 'vanishing plaques' may still be present at the microscopic level. After an interval of only 3 months, the conclusion that such lesions have disappeared from the brain may, therefore, be premature.

We have shown that gliosis produces a mild abnormality of the signal intensity of white matter on IR and short $T_E$ SE images, without corresponding changes on the longer $T_E$ (e.g., 120 ms) SEs. These findings are consistent with an increase in proton density (and therefore water content) and $T_1'$, but little change in $T_2'$. Confirmation that the latter had remained stable was provided by measurement of $T_2'$ and is consistent with the findings of Parrish *et al.* (1974). By contrast, oedematous cerebral lesions are most clearly demonstrated by heavily $T_2$-weighted imaging sequences (Smith *et al.*, 1985), and show corresponding increases in $T_2'$ (Barnes *et al.*, 1987). Thus the respective findings of the studies on the acute and chronic phases of the cold lesion indicate that the numerical relationship between $T_1'$ and $T_2'$ provides a basis for differentiating between predominantly gliotic lesions and those containing significant amounts of oedema.

An increase in tissue water generally causes a corresponding increase in the relaxation times (Mathur-De Vré, 1984). This effect is consistent with the MRI appearances of an increase in proton density, and the measured increase in $T_1'$ of gliotic tissue in these experiments. The differential effects on $T_1'$ and $T_2'$ of oedema and gliosis may be related to the different physicochemical environment of tissue water in each. Whereas oedema fluid is mostly unbound to tissue macromolecules (Faruse *et al.*, 1984), intracellular water within the astrocytic processes, which occupy most of the gliotic white matter, is closely related to densely packed glial fibrils and other cytoplasmic structures. This association would be expected to increase the efficiency of spin-spin more than spin-lattice relaxation (Berendsen, 1975), thereby resulting in a shortening of $T_2'$ relative to $T_1'$, as we have observed in the gliotic white matter.

In patients with MS, the cerebral abnormalities demonstrated by MRI generally show a more abnormal signal intensity, particularly in heavily $T_2$-weighted images (Runge *et al.*, 1984), than those observed in the present experiments on gliosis uncomplicated by demyelination or oedema. This discrepancy may be due to pathological differences, volume averaging of heterogeneous tissues in the images, or a combination of these factors. Volume averaging could not be excluded in the present experiments, although every attempt was made to minimize it. The suprasylvian gyrus was chosen for lesioning because anteroposteriorly the white matter within and beneath it is uniform for about 1 cm. Furthermore, in each animal the anteroposterior extent of the pathological changes (6–9 mm) was greater than the MRI slice thickness of 5 mm, and both were centred on the cortical lesion. It is therefore likely that the difference in the MRI appearances of uncomplicated gliosis and MS lesions are due primarily to pathological factors. Properties of the tissues which might influence their NMR characteristics in this way include a difference between them in free water content, and the absence of myelin in MS lesions (E. Herbe *et al.*, personal communication 1986).

Determination of the $T_2$ MD characteristics of a tissue can provide further information about the physical environment of the water within it. The finding of a significantly biexponential $T_2$ decay function implies that at least two separate water compartments are unable to exchange with each other on the time scale of their $T_2$ relaxation times. The most clear compartmentalization effect in biological systems is between the intracellular and extracellular spaces. In previous studies it has been found that normal white matter may yield a biexponential $T_2$ decay (Parrish *et al.*, 1974; Bakay *et al.*, 1975; Barnes *et al.*, 1987). This finding suggests that diffusion of water molecules proceeds relatively slowly across the myelin sheath which acts to separate the major tissue water compartments. This interpretation is in keeping with the axonal shrinkage which follows demyelination, which Prineas and Connell (1978) suggested was due to loss of water from the axon. Further evidence for this conclusion has been provided by NMR studies of vasogenic oedema in which the extracellular space is considerably enlarged. In this tissue, Naruse *et al.* (1986) observed a clearly biexponential $T_2$ decay, and assigned the components to intra- and extracellular water.

In the present experiments, gliosis yielded a monoexponential $T_2$ decay in each case. In this tissue the size of the extracellular space is unknown, but was seen to be obliterated at many points by the presence of junctional complexes between processes, and it was never enlarged. Furthermore, only a single plasma membrane separates intracellular and extracellular water. These considerations make it unlikely that gliotic tissue, in the absence of significant amounts of oedema, would show biexponential $T_2$ relaxation. Oedema may, however, be present in pathologically active chronic MS lesions (Prineas and Connell, 1978). Our observations suggest that quantitative MRI techniques might provide a means of assessing the natural history, current pathological activity, and response to treatment of lesions in MS. The validity and usefulness of this approach are currently under investigation.

## APPENDIX

The field of view of the NMR images was 15 cm, and the data acquisition matrix was 256 × 256 with two signal averages. All scans were single 5 mm slices. A saddle-shaped receiver coil, 10 cm in diameter, was used. Accurate repositioning of the animals in the magnet was achieved by means of lasers attached to the gantry of the imager

Most spin echo (SE) images were acquired with a Carr-Purcell-Meiboom-Gill sequence which produced a train of 30 echoes at 40 ms intervals. The echo time ($T_E$) therefore ranged from 40 to 1200 ms. The repetition time ($T_R$) was 2.5 s. The inversion times ($T_I$) of the IR sequences ranged from 100 to 700 ms, and $T_R$ was 2 s. The envelope of all 90° pulses was an apodized SINC function with six zeros, giving an approximately rectangular slice profile. All 180° pulses were $90°[x] - 180°[y] - 90°[x]$

composite pulses (the letters in brackets refer to the axis around which nutation occurs). This type of pulse is more tolerant of variations in RF amplitude than conventional pulses.

*Relaxation time images*

The $T_1'$ images were always generated from an $SE_{2000/40}$ and an $IR_{2000/700/40}$ sequence, and the $T_2'$ images from an $SE_{2000/40}$ and an $SE_{2000/120}$ image. These images were formed using the manufacturer's algorithms which are based on standard equations. The accuracy of the relaxation times derived from these images was investigated using gels of known $T_1$ and $T_2$: no systematic error was observed for the range of $T_1$ between 200 and 1500 ms. $T_2$ was underestimated by about 5% for values between 50 and 400 ms. No significant nonuniformity could be detected in relaxation time images of uniform test objects (containing manganese chloride solutions) over the volume occupied by the heads of the animals.

*Magnetization decay curves*

$T_2$ MD curves were constructed from signal intensity readings taken from regions of interest in each SE image generated by the CPMG sequence. $T_2$ MD curves from monoexponential test objects filled with manganese chloride solutions showed no systematic deviations from linearity to $T_E$ values of 1 s (echo number 25). Longer $T_E$ images do have noticable artefacts (probably due to imperfections in RF pulses and gradient eddy currents), and the MD curve is correspondingly degraded. No tissue measurements were taken from these images.

The number of data points which can be acquired from tissues depends on the rate of signal decay in the region of interest, in the present experiments, the MD curves from abnormal white matter were composed of 8–10 points. An iterative computed least-squares fitting procedure was then applied to the data. Best fits were sought for the following mono- ($F_M$) and biexponential ($F_B$) decay functions:

$$F_M = S \exp(-T_E/T_2)$$

$$F_B = S_a.\exp(-T_E/T_{2a}) + S_b \exp(-T_E/T_{2b})$$

where S is the initial signal intensity for the monoexponential decay; $S_a$ and $T_{2a}$ are the initial intensity and $T_2$, respectively, of the short $T_2$ component, and $S_b$ and $T_{2b}$ are the corresponding parameters of the long $T_2$ component for the biexponential decay Measurements on monoexponential test gels of known $T_2$ have shown that this procedure gives no significant inaccuracy between $T_2$ values of 50 and 250 ms.

In general a biexponential fit will yield a smaller residual sum of squares than a monoexponential fit. The statistical significance of this improvement can be assessed using an F-test (Bevington, 1969). We have previously found that a biexponential function can be found for a tissue using our least-squares fitting algorithm even when it does not offer a significant improvement over the monoexponential function (Barnes *et al.*, 1987). The inability of the algorithm to converge on a biexponential function can, therefore, be taken to indicate a monoexponential $T_2$ decay.

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# THE LOCALIZATION OF THE LESION IN PATIENTS WITH ACUTE OPHTHALMOPLEGIA, ATAXIA AND AREFLEXIA (MILLER FISHER SYNDROME)

## A SERIAL MULTIMODAL NEUROPHYSIOLOGICAL STUDY

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## SUMMARY

Results of comprehensive serial neurophysiological tests from onset to full recovery in 3 patients with the Miller Fisher syndrome (acute ophthalmoplegia, ataxia and areflexia) are presented. These included EMG and nerve conduction, late response (H and F wave) and direct facial motor and blink reflex studies, computerized motor unit number estimation, automated quantitative sensory threshold measurements, quantitative pupillometric and pupillopharmacological studies and multimodality evoked potential (VEP, SEP and BAEP) and EEG recordings. The results provided unequivocal evidence of peripheral nerve dysfunction. Improvement of the peripheral neurophysiological parameters accompanied or followed clinical recovery in all 3 patients. No abnormality in the CNS pathways investigated by these tests was found. The findings support the conclusion that this syndrome is to be included within the spectrum of acute inflammatory polyneuropathy. The value of serial measurements in detecting milder peripheral nerve lesions is emphasized.

## INTRODUCTION

In 1956, Miller Fisher described an acute neurological illness with a benign course characterized by ophthalmoplegia, ataxia and areflexia. On the basis of an increase of the cerebrospinal fluid (CSF) protein content unassociated with pleocytosis, the author regarded the entity to be a variant of the Guillain-Barré syndrome. Earlier but less well documented similar cases had been reported (Collier, 1932; Van Bogaert and Maere, 1938). At least 80 further cases have been described since Fisher's description in 1956 (Elizan *et al.*, 1971; Becker *et al.*, 1981; Al-Din *et al.*, 1982, 1985; Ropper and Shahani, 1983; Meienberg and Ryffel, 1983; Jamal and MacLeod 1984; Phillips *et al.*, 1984; Schapira and Thomas, 1986; Vincent and Vincent, 1986).

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The aetiology and pathogenesis of the Miller Fisher syndrome is, however, not well understood and in particular the location of the pathological changes has been the subject of controversy. Some authors have considered that the syndrome is related to acute inflammatory polyneuritis and that the pathological lesions are localized to the peripheral nerves or nerve roots (Fisher, 1956; Munsat and Barnes, 1965; Elizan *et al.*, 1971; Ropper, 1983). Others have implicated an inflammatory brainstem lesion (Bickerstaff, 1957, 1978; Al-Din *et al.*, 1982; Meienberg and Ryffel, 1983; Meienberg, 1984) or a combination of central brainstem and peripheral lesions (Van Allen and MacQueen, 1964; Green, 1976; Becker *et al.*, 1981). Arguments for speculation on the site of the lesion in the Miller Fisher syndrome are, however, based mainly on clinical observations rather than clinicopathological correlation because of the benign nature of the illness. Conventional motor and sensory nerve conduction and EMG studies were reported to be normal in several patients with the Miller Fisher syndrome (Gibberd, 1970; Tripp and Brett, 1975; Marks *et al.*, 1977; Storey *et al.*, 1977; Price *et al.*, 1978; Al-Din *et al.*, 1982, 1985; Meienberg and Ryffel, 1983). These conventional studies, however, test the distal segments of peripheral nerves of the extremities and are insensitive to abnormalities of their proximal segments. Moreover, they were performed once in each patient in the course of their illness. Despite this, some abnormalities have been recorded in a few patients with the Miller Fisher syndrome using these conventional studies. Elizan and her coworkers (1971) showed 'prolonged distal latencies' in one patient and Guiloff (1977) demonstrated abnormality of the sensory nerve action potentials (SNAPs) in 2 patients. However, it has been remarked that these abnormalities were demonstrated in atypical examples of the syndrome who had clinical evidence of marked peripheral neuropathy, whereas the majority of Miller Fisher syndrome patients do not have clinical evidence of such dysfunction (Meienberg and Ryffel, 1983; Meienberg, 1984; Al-Din *et al.*, 1985). By serial application of these conventional studies, Jamal and MacLeod (1984) demonstrated convincing evidence of significant peripheral nerve dysfunction in a typical case of the Miller Fisher syndrome who had no clinical evidence of sensory changes or motor weakness. Improvement of the peripheral nerve parameters in their patient accompanied or followed clinical improvement. The combination of conventional neurophysiological methods with some recently introduced more sophisticated techniques have proved useful for the detection, localization and quantification of disturbances of function in the peripheral nervous system, including the most proximal inaccessible segments, and in the CNS, including various pathways in the brainstem. In this study we present the results of the serial application of these multimodal neurophysiological techniques in 3 classical cases of the Miller Fisher syndrome and discuss these results in the context of peripheral versus CNS involvement.

## CASE REPORTS

### *Case 1*

This 21-yr-old male presented with sudden onset of diplopia and ataxia of gait Two weeks before, he had developed a sore throat and abdominal, neck, shoulder and arm pain. On examination he had an incomplete left ptosis. Movements of both eyes were restricted in all directions but abduction was relatively less affected. Both pupils were dilated and reacted poorly to light and on accommodation. Speech was nasal and palatal movements were absent but palatal sensation was intact. Power and sensation in the limbs were normal. He had marked ataxia of gait but minimal incoordination of the limbs and no tremor was present. All tendon reflexes were absent. Routine haematological and biochemical investigations, x-ray examination of chest and skull and CT scan of the head were all normal. Virological studies showed a positive EB virus IgM The CSF was under normal pressure and showed an increased protein content (0.8 g/l) with a normal cell count.

Spontaneous recovery began 12 days after presentation. His gait improved steadily and was normal 1 month after the onset of the illness Eye movements and pupillary responses started to improve at day 18 and were almost normal 30 days after the onset of symptoms when the patient still had some double vision on extreme lateral gaze and a few beats of nystagmus in the abducting eye on right lateral gaze. These abnormalities had disappeared when examined 60 days after the onset. Tendon reflexes remained absent until 4 months after the onset of the illness.

### *Case 2*

A 56-yr-old man presented with a 1 day history of severe limb and trunk ataxia, tingling in the hands, diplopia and bilateral symmetric ptosis. Ten days before he had an influenza-like illness with sinusitis. On examination he had diplopia on lateral gazes with severe limitation of eye movements in all directions. Pupil sizes were normal and equal and reacted normally to light and on accommodation. All tendon reflexes were absent. His gait was ataxic to such a degree that he was unable to walk unaided and he was incoordinate in performing finger-nose and heel-shin tests. Power and sensation were normal. Two days after admission palatal and a minimal right-sided facial weakness appeared.

Investigations, including haematological, biochemical, virological, radiological (of chest and skull) and CT scan of brain, were normal. The CSF protein content was raised (1.28 g/l) with normal cell count. Within 10 days the ataxia and diplopia began to improve. He was asymptomatic 1 month later. Tendon reflexes were detectable after 2 months and became normal 4 months after the onset of the illness.

### *Case 3*

A 15-yr-old boy developed an influenza-like illness with cough and rhinorrhoea. One week later he had sudden onset of blurring of vision which rapidly progressed to diplopia, associated with bilateral ptosis and unsteadiness of gait. On admission 5 days after the onset of the neurological illness, examination revealed fixed equally dilated pupils. There was a marked restriction of eye movements in all directions with paralysis of upward movement and lateral gaze nystagmus. Mild lower motor neuron weakness of the left facial muscles was noted with palatal weakness and a nasal quality to the speech. There was complete areflexia. There was severe gait and truncal ataxia with inability to walk or sit unaided, but only minimal limb incoordination and no abnormality of other cerebellar functions was present. No limb weakness or sensory dysfunction was detected on clinical examination. The only abnormality on investigation was an increased CSF protein content (0.99 g/l).

Improvement occurred within 10 days of the onset of the neurological symptoms when the ataxia and nasal speech became less severe and disappeared within 14 days of the onset of the illness. The eye movements and pupillary responses progressively improved and at 3 months were normal. When examined 6 months from the onset of the illness the patient was still areflexic but otherwise normal.

## RESULTS

### *Neurophysiological investigations*

Serial multimodal neurophysiological tests were performed on all 3 patients within 1 week of the onset of the neurological manifestations and repeated at 1 month, 2 months, 4 months and 6 months. All investigations were undertaken at a controlled room temperature of 22 ± 2° C. The limbs examined were maintained at 34 ± 1° C via a thermostatically controlled heating lamp. The results of these tests were compared with the range of normal values for our laboratory for each specific test. Limits of normal were determined by the application of a 99% confidence limit to a nonpatient control population for each test with the exception of motor and sensory conduction values where a 95% confidence limit was applied in keeping with the convention in the literature.

*Electromyography* (*EMG*). Concentric needle EMG recordings were obtained from the right extensor digitorum brevis (EDB) the right tibialis anterior muscles and the first dorsal interosseous of the right hand. No abnormal spontaneous activity was found at rest and individual motor unit potentials had normal amplitude, duration and waveforms. The recruitment patterns were normal. Facial muscle EMG failed to reveal any abnormality in all 3 cases.

*Nerve conduction velocity studies.* Shortest distal motor latencies (SDMLs) and fastest motor nerve conduction velocities (FMNCVs) were within the normal limits in all 3 cases for the right common peroneal, right ulnar and right median nerves (fig. 1). On subsequent tests, however, all FMNCVs increased and SDMLs decreased progressively (fig. 1). These improvements were significant when compared with the normal variance of multiple testing of age and sex-matched controls ($P < 0.01$). Serial studies of orthodromically evoked sensory nerve action potentials (SNAPs) for the right sural, ulnar and median nerves showed some initial abnormalities of amplitude, latency and duration with subsequent progressive improvement (fig. 2).

*Late response studies.* Latency of H reflex (Hoffmann, 1922) from the right posterior tibial nerve (Kimura, 1983*c*) and F waves from the right posterior tibial, right common peroneal and right median and ulnar nerves (Kimura, 1983*b*) were recorded using conventional methods. Changes in the H reflex are summarized in the Table. These were absent in Cases 1 and 2 until 2 months after onset when they showed a progressive decrease in latency and increase in amplitude eventually to lie within normal limits by 6 months. In case 3 the H reflex remained absent at 6 months but when the patient was seen 18 months after the onset of his neurological illness it was found to be present and normal. The shortest of 10 F wave latencies was measured using supramaximal stimulation as recommended (Kimura, 1983*b*). These also showed abnormalities at the onset of the illness with rapid and progressive improvement subsequently (fig. 1).

*Facial nerve conduction and blink reflex studies.* Direct (D) facial responses and blink reflex studies were performed on all 3 patients with similar time sequences to the H and F responses using standard methods (Kimura, 1983*a*). Care was taken

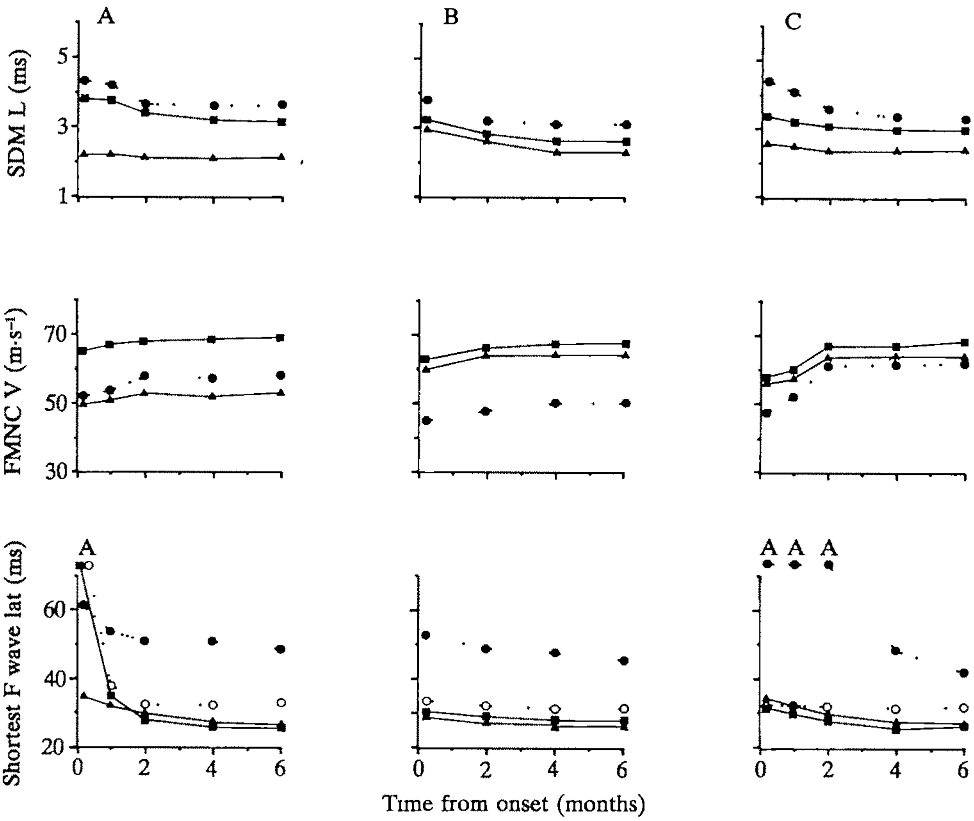

FIG 1 Results of serial motor nerve conduction and F wave studies in *Cases 1–3* (A–C, respectively) Values for shortest distal motor latency (SDML) and fastest motor nerve conduction velocity (FMNCV) were initially within the range of normal but showed progressive improvement on serial testing. F waves were initially absent or their latency abnormally prolonged with subsequent improvement to normal values on serial studies. ▲ = ulnar nerve; ■ = median nerve, ● = peroneal nerve, ○ = tibial nerve, A = absent

to use the same optimum intensity electrical shocks on both sides to produce maximum and stable responses. At least 10 stimulations on each side were applied and the shortest latency of R1 and R2 responses were recorded from the stimulus artefact to initial deflection of the evoked potentials. The D responses from the facial muscles were obtained by stimulating the respective facial nerve and recording from the ipsilateral orbicularis oculi muscle using surface electrodes. These studies showed abnormalities in Cases 2 and 3 but were normal in Case 1. Fig. 3 illustrates these results for Case 3. The initially prolonged R1 latency, mainly on the left, is shown to return to normal on subsequent testing. The latency of R2 on the left is consistently and about equally prolonged on ipsilateral or contralateral stimulation. All latencies became normal in the study performed 2 months after the onset of the illness. Improvement in these responses was also accompanied by some

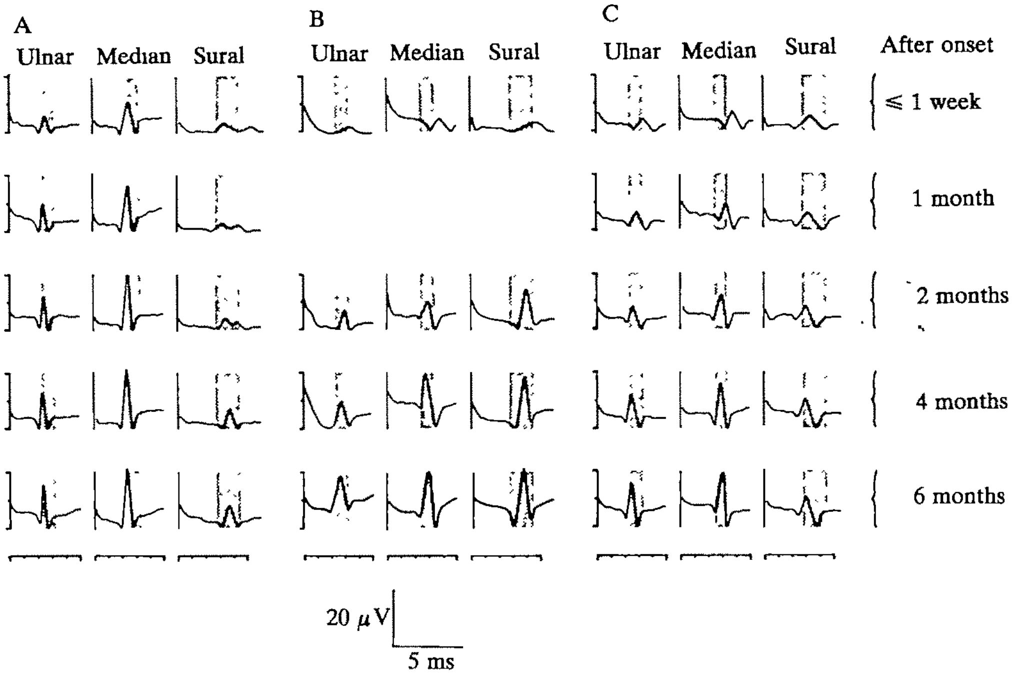

FIG 2 Results of serial sensory nerve action potential studies on the right in *Cases 1–3* (A–C, respectively) The shadowed bars represent the range of normal negative peak latency. Definite abnormality in some of the potentials was present initially but progressive improvement in their amplitude and peak latency was seen on serial testing

TABLE. H REFLEX LATENCY (ms) IN 3 PATIENTS WITH THE MILLER FISHER SYNDROME

| *Time after onset* | *Case 1* | *Case 2* | *Case 3* |
|---|---|---|---|
| 1 week | Absent | Absent | Absent |
| 1 month | Absent | Absent | Absent |
| 2 months | 40 | 38 4 | Absent |
| 4 months | 36 | 38 | Absent |
| 6 months | 35 | 32 8 | Absent |
| 18 months | ND | ND | 34 6 |

ND = not done

improvement of the D response particularly from the left side in terms of latency and duration.

Similar changes were found in the studies of Case 2 (prolongation of latency of R1 on the right and consistent prolongation of R2 latency and reduction of its amplitude on the right with stimulation on either side) but, in addition, the D response on the right was abnormally prolonged in latency and duration. These changes also progressively improved to lie within the normal limits in the study performed 2 months after the onset of symptoms.

*Motor unit number and motor unit potential (MUP) analysis.* This computer

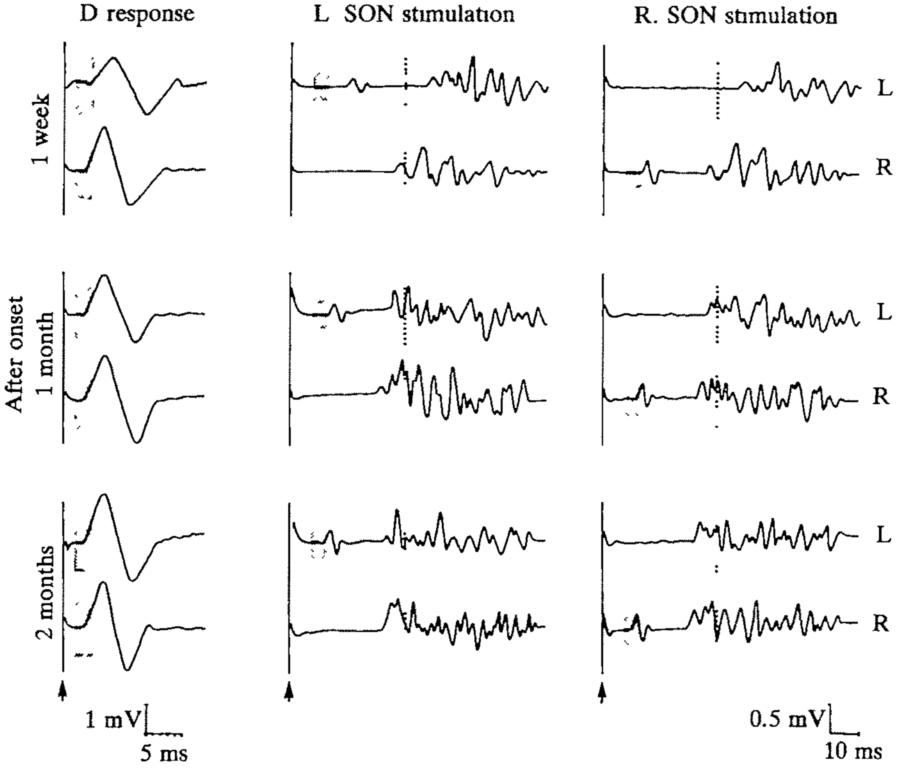

FIG. 3. Serial direct facial motor responses (D response), to facial nerve stimulation, and blink reflex studies to supraorbital nerve (SON) stimulation, recorded using the same setting of recording electrodes from orbicularis oculi muscles (Kimura, 1983*a*) in *Case 3*. Shadowed bars represent the normal range of onset latency for R1 and D responses and vertical dotted lines represent the upper limit of normal onset latency for R2 responses

method for estimating the number of motor unit potentials (MUPs) and the analysis of their mean parameters in the EDB muscle using surface recording has been discussed in detail elsewhere (Ballantyne and Hansen, 1974*a,b*). These studies were performed in Cases 2 and 3 at presentation at 1 week from the onset and also 6 months from the onset. In Case 2, motor unit numbers were estimated to be 40 and rose to 97 when repeated after 6 months. In Case 3, motor unit numbers rose from an initial estimation of 74 to 217. Both these changes were well outside the 99% confidence limit derived from application of this technique to a normal control group (Ballantyne and Hansen, 1974*a*).

*Evoked potential studies.* Evoked potential testing was performed using the Medelec Sensor System (Medelec Ltd., UK). The 10–20 international system of electrode placement was used (Jasper, 1958).

Upper extremity somatosensory evoked potentials (SEPs) to median nerve stimulation (Jones, 1982) at the wrist were abnormal in all 3 cases on presentation. Fig. 4 shows the results of the SEP studies in Cases 1 and 3. In Case 1, the Erb's point potential (EP) was normal but the EP-spinal (N13) conduction time was abnormally

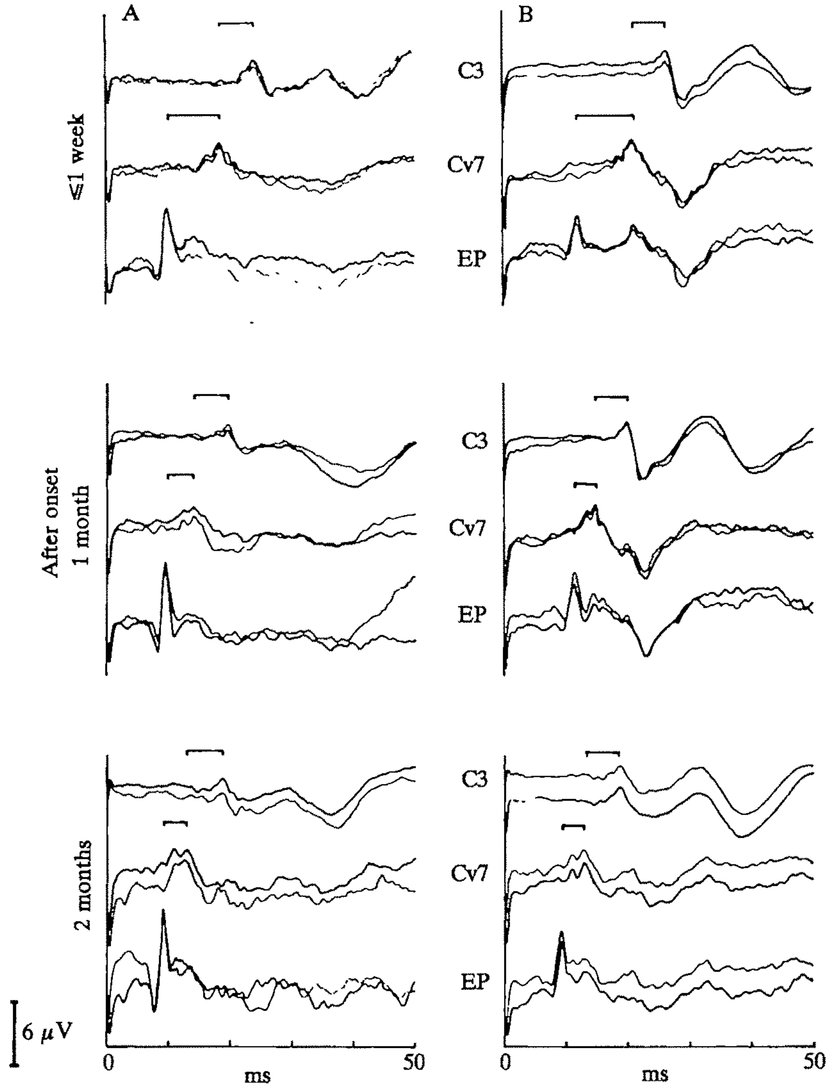

FIG 4 Serial somatosensory (SEP) recordings with right median nerve stimulation at wrist in *Cases 1* (A) and *3* (B). Recording electrodes were referred to an Fz electrode and each trace is from 512 averaged sweeps EP-N13 conduction time was abnormally long initially with progressive improvement on serial testing whereas N13–N20 (central) conduction time was normal and remained relatively unchanged in both patients C3 = third cervical vertebra, EP = Erb's point, Cv7 = seventh cervical vertebra.

prolonged while the N13–N20 central conduction time was within normal limits. In addition to the prolongation of EP-N13 conduction time in Case 3 the EP potential was small in amplitude and prolonged in latency. In Case 2, the SEP findings were similar to those in Case 3.

Brainstem auditory evoked potentials (BAEPs) were performed using standard methods (Chiappa *et al.*, 1979). On presentation and at all subsequent examinations in all 3 patients waves I–V were identified with normal latencies. Interwave peak latencies (I–III, III–V, I–V) were all normal and did not change on repeated measurements. No significant side-to-side differences were noted.

Serial recording of pattern reversal visual evoked potentials separately to each eye were also carried out using standard methods (Halliday *et al.*, 1972). The triphasic negative-positive-negative response in the Oz-Fz derivations were identified in each patient and their latencies, amplitudes and waveforms were normal and symmetric on presentation and subsequently.

*Electroencephalography* (EEG). Serial 16 channel EEG recordings showed no abnormality in any of the patients.

### *Quantitative studies of somatic sensation*

*Thermal sensation.* Thresholds for the appreciation of heat and cold were determined for the volar aspect of the wrist just proximal to the distal wrist crease and for the medial aspect of the right ankle behind the medial malleolus. Thresholds were expressed as temperature change in deg C from a fixed basic skin temperature. These measurements were performed using a microprocessor controlled system and the two-alternative forced-choice method (Jamal *et al.*, 1985*a*, *b*). These thresholds were initially abnormally high at the ankle in all patients but subsequently returned to normal on repeated longitudinal studies (fig. 5).

*Vibration sensation.* Vibration perception threshold (VPT) was also measured serially in all 3 cases on the dorsal aspect of the right second metacarpal bone and on the dorsomedial aspect of the middle of the right first metatarsal bone using the technique of Goldberg and Lindblom (1979). Threshold values were given as the minimum displacement amplitude in $\mu$m applied by the vibrator at 100 Hz which gave rise to the sensation. The results are summarized in fig. 5. VPTs were abnormally increased initially but returned to normal values within 2 months from the onset of the Miller Fisher syndrome.

### *Pupillometric studies*

*Method.* Pupillary diameter and reflex abnormalities were studied quantitatively using an improved photographic method recently described with control values from this department (Ramsay and Woodruff, 1987). The following is a summary of the method. The photographic apparatus included a Minolta X700 camera body programmable to take photographs at given intervals with a flare-free flash illumination of 0.016 s duration from a Minolta PX 360 flash gun. Since this duration is shorter than the light reflex latency (0.2 s) (Lowenstein and Loewenfeld, 1962), isolated measurements of pupillary diameter were not affected by flash illumination of the eye (Ramsay and Woodruff, 1986).

The patient's eyes were photographed while seated at an ophthalmic table and the vertical pupillary diameter was then measured from the enlarged negative and corrected to real values using the appropriate magnification factor. Each measurement of pupil diameter was expressed to the nearest 0.1 mm. Sequential exposures, timed to monitor changes in pupillary diameter in response to an abrupt transition from light to dark (the dark reflex) or to sudden alteration of visual fixation point (the accommodation reflex), were taken. The pupillary darkness reflex was assessed by taking a train of 8 flash exposures at 5 s intervals, the first two of which were taken in bright light (provided by a

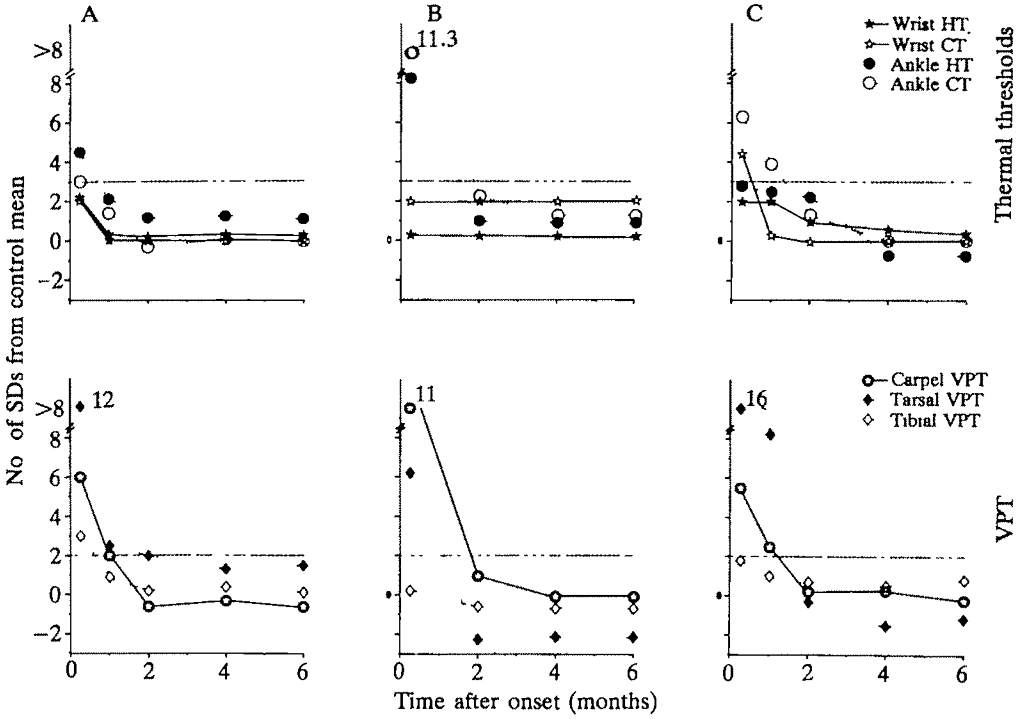

FIG. 5 Serial thermal and vibration perception threshold (VPT) measurements in *Cases 1–3* (A–C, respectively). HT = heat threshold; CT = cold threshold Each threshold value is expressed as a figure representing the number of standard deviations from the mean control value (represented as zero value). Ordinates show these values (negative below mean and positive above mean control value for that test). The upper limit of normal threshold measurements are indicated by the horizontal interrupted lines

light with a conical reflector, cone base diameter 15 cm, and a 100 Watt light bulb with the opening of the reflector 70 cm from the subject's face) The light was then extinguished at the instant of the second exposure so that the following 6 exposures were taken in darkness. Two additional flash exposures were then taken in continuing darkness 30 s and 60 s after the last of the 8 exposure train. The patient was asked to hold his gaze on a standard fixation point (a dim red light emitting diode 270 cm away) throughout this sequence.

The pupillary accommodation reflex was assessed in a 12 flash exposures under subdued light conditions, at 2 s intervals The patient was asked to fix his gaze on the standard fixation target until the instant of the fourth flash when he moved visual fixation to a near point 18 cm away from the eye in line with the optical axis of the camera lens with his nasal bridge. At the instant of the eighth flash he would return his gaze to the standard far fixation target 270 cm away.

Irideal neurotransmitter sensitivity was also measured using this method to study any defects of autonomic innervation of iris muscles. Abnormalities of these reflexes and sensitivity were identified at values beyond the 99th centile derived from the application of the methods to 40 normal subjects (Ramsay, 1986; Ramsay and Woodruff, 1987). Irideal cholinergic parasympathetic sensitivity was assessed by measuring the degree of pupillary constriction 30 min after the administration of two drops of freshly prepared 0.05% pilocarpine solution to both conjunctival sacs in uninterrupted darkness (Cohen and Zakov, 1975). In the 40 control subjects, a decrease in pupillary diameter greater than 1.4 mm in darkness in response to 0.05% pilocarpine was abnormal (Ramsay, 1986).

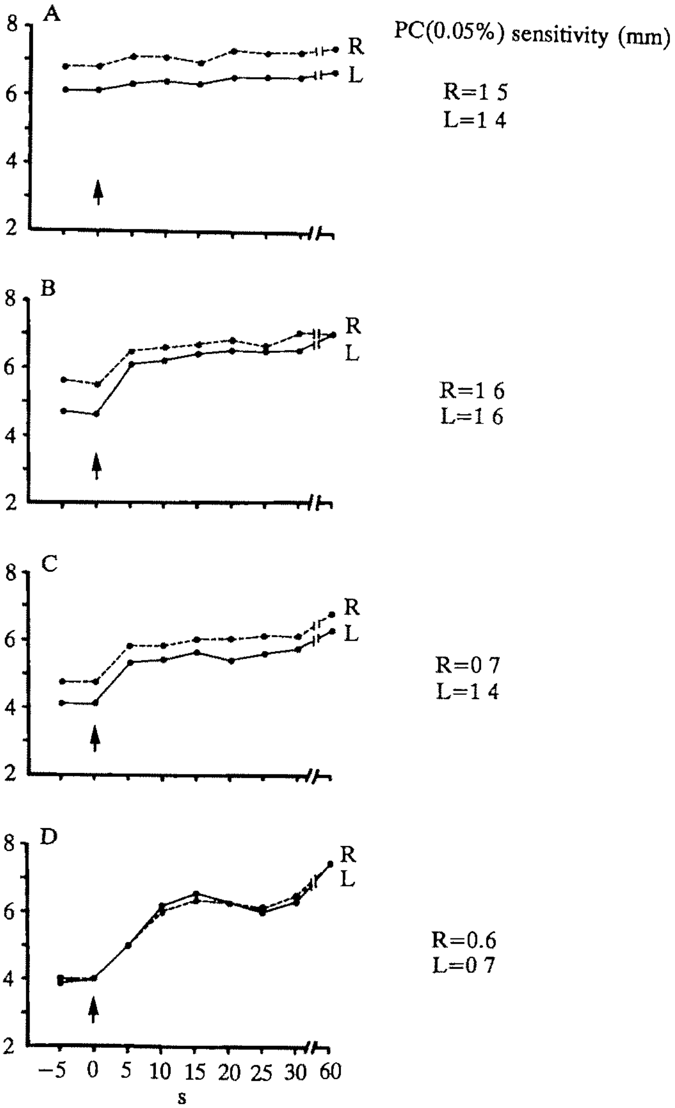

FIG. 6 Serial quantitative studies of pupillary darkness reflex and pupillary cholinergic (PC) sensitivity in *Case 3* at 1 week (A), 1 month (B), 2 months (C) and 6 months (D). Arrows indicate the onset of complete darkness. Ordinates represent vertical pupillary diameter in mm. Both PDR and pupillary cholinergic sensitivity were abnormal initially and returned to normal after 6 months.

*Results.* Darkness reflex and pupillary neurotransmitter sensitivity studies in Case 3 are summarized in fig. 6. At the onset of the illness both pupils were abnormally large and as a consequence, the amplitude of the darkness reflex was diminished. At this stage the right pupil was supersensitive to pilocarpine while the response of the left pupil was at the upper limit of normal (fig. 6). Within a month, however, considerable recovery had occurred in the darkness reflex but

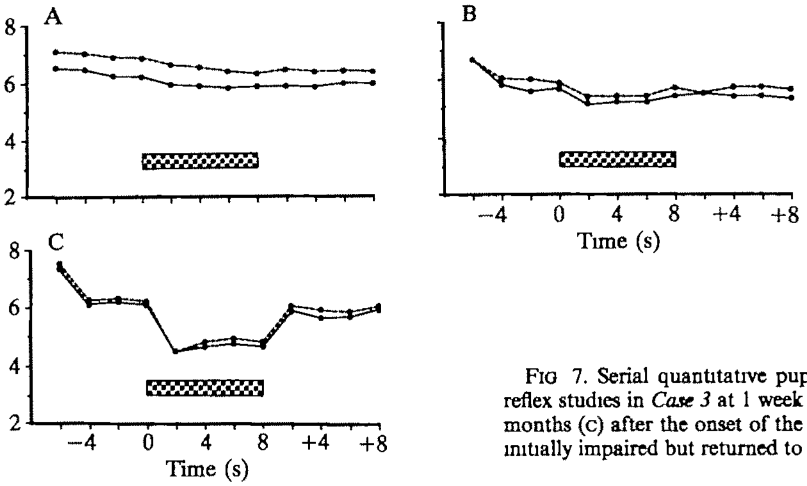

FIG 7. Serial quantitative pupillary accommodation reflex studies in *Case 3* at 1 week (A), 1 month (B) and 6 months (C) after the onset of the illness This reflex was initially impaired but returned to normal by 6 months

the sensitivity of the pupils to pilocarpine had increased and both pupils were supersensitive. Subsequently a small improvement in the darkness reflex was demonstrable though anisocoria remained and the pupillary pilocarpine sensitivity waned to normal values, though significant side-to-side differences between the two pupils were still present at 6 months after the onset (fig. 6). Shortly after the onset both pupils constricted in response to 4% pyridostigmine by 4.5 mm on the right and 4.9 mm on the left. Irideal adrenergic sensitivity was not tested in the patient as the base-line size of the pupils was large and this will influence its measurements (Bourgon *et al.,* 1978). Thus the measurable effect of phenylephrine on a large pupil, as in Case 3, is necessarily limited since, irrespective of the true adrenergic irideal sensitivity, the pupillary size before drug application is close to the anatomical limit for dilatation of the sphincter pupillae. Pupillary constriction to near vision, the accommodation reflex, was impaired shortly after the onset but considerably improved one month after and was normal five months later (fig. 7).

### *Radiological studies*

CT cranial scans were undertaken in all 3 patients and were normal in each.

## DISCUSSION

The results of serial multimodal neurophysiological tests in our 3 patients, each with a typical Miller Fisher syndrome, provide evidence of peripheral nerve dysfunction. Neither the neurophysiological investigations nor CT scans of the head produced evidence of abnormality in the CNS. Improvement in the neurophysiological parameters of peripheral dysfunction followed or accompanied clinical recovery in all 3 cases.

Motor conduction velocities in the distal portions of the peripheral nerves were initially within the normal range but subsequently increased, while the shortest distal motor latencies decreased in subsequent studies in all three nerves examined (fig. 1). Significant abnormality of F wave latency, however, was present in all 3 patients (fig. 1). The more marked abnormality of the F waves compared with the motor conduction velocities suggests a more significant block of conduction at the level of the spinal roots, limb girdle plexuses or proximal segments of the nerve (Kimura and Butzer, 1975; Shahani *et al.*, 1980; Ropper and Shahani, 1984). The considerable prolongation of F wave latencies (seen initially or later during recovery) is suggestive of demyelination of the proximal segments (Kimura, 1983*b*) and the return of F wave latencies to normal values indicates recovery of conduction across these proximal segments of the nerve (Kimura, 1983*b*).

Prolongation of F wave latency or absence of the response are frequently seen in patients with the Guillain-Barré syndrome early in the course and may be the only abnormality in their peripheral nerve motor studies (Kimura and Butzer, 1975; Shahani and Young, 1983; Ropper and Shahani, 1984). The H reflex was absent in all 3 patients until the examination at 2 months (Cases 1, 2) and at 18 months (Case 3) when it reappeared with a progressive decrease in its latency (*see* Table). H reflex latency is a measure of conduction velocity in the proximal segment of the tibial nerve (Kimura, 1983*c*). Whether this slowing is due to a lesion in the sensory or motor fibres, or both, is unknown, but the absence of a significant limb weakness in our patients and the normal F wave latency in the tibial nerves in Cases 2 and 3 with absent H reflex might favour abnormality in the afferent fibres of the reflex arc. Reduction of peak-to-peak amplitude, prolongation of the peak latency and abnormal dispersion of the sensory nerve action potentials was seen to some extent in all 3 patients, and all of these parameters progressively improved on serial measurements (fig. 2). Dispersion of sensory action protentials usually arises as a result of asynchronization of the afferent volley due to differential demyelination in the large diameter sensory fibres (Buchthal *et al.*, 1984). Demyelination will also result in diminution of the amplitude and prolongation of the latency of the potential (Buchthal *et al.*, 1984).

The results of the estimations of motor unit numbers carried out in 2 of our 3 patients showed a reduction in motor unit numbers indicating loss of function in peripheral motor nerve fibres to the extensor digitorum brevis muscle. Significant rises in motor unit numbers were noted in both these patients (in Case 2 to just below normal and in Case 3 to normal values) at 6 months after the onset of the illness. These findings are very similar, albeit milder, to the results of sequential studies in the Guillain-Barré syndrome (Martinez-Figueroa *et al.*, 1977; Hansen *et al.*, 1982) using the same technique. The reduction in motor unit numbers is likely to be due to demyelination and conduction block of individual motor axons to the EDB muscle and this may not be reflected in conventional conduction studies. The significant increase in the number of functioning motor axons to the EDB in these 2 patients over a period of 6 months indicates reversibility of the underlying pathology and a progressive return of function is probably from remyelination in the peripheral motor nerves to these muscles. This is further clear evidence of peripheral motor nerve involvement in the Miller Fisher syndrome.

The consistent prolongation of R2 from the left side regardless of the site of stimulation in the blink reflex studies in Case 3 (fig. 3) suggests abnormality of conduction in the efferent arc (the left facial nerve) and in view of the normal direct response latency (fig. 3) the proximal part of the left facial nerve is the probable site of the lesion. This was confirmed by simultaneous recording of R2 components in both sides in response to a glabellar tap, which stimulates both trigeminal nerves simultaneously, each of which activates the facial nuclei on both sides (Kimura, 1983*a*). A consistent prolongation of R2 latency on the left was seen, confirming the abnormality in the left facial nerve (Kimura, 1983*a*). Gradual recovery in blink reflex studies accompanied clinical improvement of the left facial weakness. Similar abnormalities of the blink reflex have been noted in patients with the Guillain-Barré syndrome (Shahani and Young, 1983; Kimura, 1983*a*). An important finding on the SEP studies was the prolongation of the Erb's point to spinal (N13) conduction time with normal central (N13–N20) conduction (fig. 4). EP-N13 conduction time provides a measure of conduction in the large diameter sensory fibres in the most proximal parts of the brachial plexus and the cervical roots (Desmedt and Noël, 1973; Jones, 1979). Subsequent tests showed gradual improvement of the SEP studies (fig. 4). Similar findings have been noted in 25% of cases of the Guillain-Barré syndrome (W. F. Brown, M. Davis and T. E. Feasby, 1982, unpublished).

Abnormalities of the thermal and vibration perception thresholds in these patients (fig. 5) indicate dysfunction of the small fibre thermal pathway in the former (Jamal *et al.*, 1987) and of the large fibre sensory pathways in the latter (Goldberg and Lindblom, 1979). Since these techniques test the integrity of both peripheral and central pathways, the site of dysfunction can only be inferred. Both subjective and objective sensory dysfunction to all modalities has been noted before in patients with the Miller Fisher syndrome (Fisher, 1956; Elizan *et al.*, 1971; Guiloff, 1977; Ropper and Shahani, 1983). The presence of abnormalities in these tests without obvious clinical involvement in our patients probably reflects subclinical dysfunction, since loss of function in 40% of sensory fibres is present before any clinical abnormality of sensation appears (Ropper and Shahani, 1984). The abnormally dilated pupils and the low amplitude darkness reflex observed earlier in the course of the illness in Case 3 (fig. 6) does resemble those observed in patients with tonic pupils (Ramsay, 1986) which are thought to be caused by postganglionic parasympathetic denervation (Loewenfeld and Thompson, 1967; Harriman and Garland, 1968). The recovery of pupillary function noted subsequently (fig. 6) accompanied improvement of the other parameters of peripheral nerve dysfunction. The patients' pupillary response to a dilute solution of pilocarpine showing increased sensitivity is consistent with a postganglionic parasympathetic lesion (Pilley and Thompson, 1975; Keane, 1977; Okajima *et al.*, 1977). Postganglionic parasympathetic oculomotor nerves are among the few myelinated fibres of the postganglionic autonomic nervous system (Warwick, 1954) and it is likely that this patient had dysfunction in these fibres similar to that observed in the other peripheral nerves. Pupillary abnormalities are encountered in about half of the cases of the Miller Fisher syndrome (Elizan *et al.*, 1971; Keane, 1977). The pupils tend to be dilated or sometimes unequal and reaction to light and accommodation is absent or limited (Keane, 1977). Irideal cholinergic supersensitivity has been reported previously in the Miller Fisher (Okajima *et al.*, 1977) and the Guillain-Barré syndromes (Keane, 1977; Williams *et al.*, 1979). Abnormality of adrenergic innervation of the iris has also been reported in the Miller Fisher (Okajima *et al.*, 1977) and the Guillain-Barré (Williams *et al.*, 1979) syndromes. In our patients the complete recovery of the SNAPs and the SEP root abnormalities, the significant slowing of F wave and H reflex latencies and their subsequent recovery, the absence of signs of denervation, and rapid clinical recovery suggest that the neuropathy is, at least predominantly, of the demyelinating type. Support for this comes from pathological findings of demyelination in the peripheral nerves in a case of the Miller Fisher syndrome (Phillips *et al.*, 1984). Patchy demyelination of the oculomotor nerves (Dehaene *et al.*, 1986) and of other cranial nerves (Phillips *et al.*, 1984) has been found in 2 patients.

All these pathological features have been described in the Guillain-Barré syndrome (Asbury *et al.*, 1969; Prineas, 1981). Overlap between the Miller Fisher and Guillain-Barré syndromes in the same patient has been reported (Elizan *et al.*, 1971; Williams *et al.*, 1979; Arnason, 1984) and suggests a similar pathogenesis underlying both disorders. A cell-mediated immunity to peripheral but not central myelin in a case of the Miller Fisher syndrome has been demonstrated (Behan and Geschwind, 1973). Findings were similar to those observed in the Guillain-Barré syndrome (Behan *et al.*, 1969; Knowles *et al.*, 1969).

The evidence for central involvement in the Miller Fisher syndrome has been based on clinical observations, ocular findings and ataxia. Many of the oculomotor signs have been considered to be due to CNS inflammation (Keane, 1977; Meienberg and Ryffel, 1983; Meienberg, 1984). Pathological studies, however, show peripheral but no CNS lesions (Grunnet and Lubow, 1972; Phillips *et al.*, 1984; Dehaene *et al.*, 1986). Much emphasis has been placed on the conjugate abnormalities of ocular movements and the pattern of ophthalmoplegia, recovery of upward before horizontal gaze, preservation of Bell's phenomenon despite impairment of voluntary upward gaze, the presence of horizontal dissociated nystagmus similar to internuclear ophthalmoplegia and mild ptosis in the presence of severe external ophthalmoplegia. All these have been held to be of brainstem origin (Jampel and Haidt, 1972; Keane, 1977; Meienberg and Ryffel, 1983; Meienberg, 1984). Ropper (1983) argued that most of these can occur in other patients with substantial peripheral lesions or in cases of non-Miller Fisher Guillain-Barré syndromes. Ropper (1983) proposed an alternative hypothesis of peripheral nerve dysfunction producing abnormal spindle input from extraocular muscles leading to disorders of afferent information producing the ocular manifestations.

The profound degree of ataxia in relation to the slight sensory and/or motor deficit has raised the question of involvement of the cerebellum or its connections in the brainstem as a possible site of involvement in the Miller Fisher syndrome (Al-Din *et al.*, 1982; Meienberg, 1984). A mechanism for this ataxia based solely on peripheral nerve dysfunction has been proposed by Ropper and Shahani (1983). The hypothesis was based on the findings of intact joint position sense with an absent proprioceptive 'silent period' or, in contrast, a normal proprioceptive 'silent period' with diminished joint position sense. Mismatching of information from muscle spindles and joint position receptors was then proposed as a possible cause for ataxia rather than a lesion in the CNS (Ropper and Shahani, 1983). This hypothesis is consistent with Richter's pathological findings (Richter, 1962) of degeneration of the fibre system of Clarke's column secondary to peripheral lesions.

Many of the signs purported to arise from a brainstem disorder can be explained on the basis of a peripheral nerve dysfunction and we believe that the evidence does not and will not support a significant central lesion in the Miller Fisher syndrome until pathological evidence counters the existing normal CNS autopsy results (Grunnet and Lubow, 1972; Phillips *et al.*, 1984; Dehaene *et al.*, 1986). It has been remarked (Ropper, 1983) that it is difficult to accept the postulation of a lesion causing all the features of the Miller Fisher syndrome in the brainstem as this has to be remarkably selective in affecting certain structures and sparing others. The normal results of central SEP conduction of BAEPs and the failure to demonstrate changes in the blink reflex studies attributable to a central abnormality would suggest a normal CNS in our patients. Our findings in these 3 cases does not exclude the possibility that associated CNS involvement may occur in some instances. However, the concept that the Miller Fisher syndrome may arise as the result of lesions restricted to or predominantly affecting the CNS cannot be accepted until supported by pathological evidence in typical instances of the syndrome.

### *Conclusion*

The results of multimodal and serial neurophysiological investigations in these 3 cases of the Miller Fisher syndrome support the thesis that the causative lesions lie in the peripheral nervous system. We have found no evidence of CNS involvement. The evidence for peripheral dysfunction reported in this study is in agreement with the conclusions derived from pathological studies in other patients. When conventional EMG, nerve conduction and other neurophysiological studies are employed, we would emphasize the superiority of sequential measurements to detect the abnormalities of peripheral nerve function in this disorder.

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# OCULAR MOTOR DEFICITS IN PARKINSON'S DISEASE

## III. COORDINATION OF EYE AND HEAD MOVEMENTS

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## SUMMARY

Eye-head coordination was measured in patients with Parkinson's disease as they made horizontal gaze shifts in response to predictable and unpredictable target steps and to targets moving smoothly with either constant or sinusoidally varying velocity. Patients preferred not to move their heads for both large and small amplitude gaze shifts. Both eye and head movement reaction times were prolonged. Saccades were hypometric and, frequently, slow. Head movements were also slow, hypometric, and varied in amplitude for target shifts of a given amplitude. Compensatory eye movements (CEMs) that normally stabilize gaze direction during head movement varied in gain from zero to greater than unity, and often drove the eyes off target. CEM abnormalities occurred most commonly in patients with abnormal vestibulo-ocular reflex (VOR) gain in darkness. We attribute these abnormalities of programming combined eye-head saccades to dysfunction of striatonigral-collicular circuits.

Smooth gaze pursuit gain, the ratio of gaze velocity to target velocity, was lowered in patients while tracking sinusoidal targets at 0.3, 0.5 and 1.0 Hz. Some patients could track these targets with the head fixed but not with the head free. We attribute this to abnormal suppression of the vestibulo-ocular reflex. The results indicate that Parkinson's disease impairs motor programming of coordinated eye-head gaze saccades and disrupts normal interaction between head movement and the VOR.

## INTRODUCTION

Rapid gaze shifts with the freely moving head are achieved by saccades coordinated with rapid head movements. Like saccades, the peak velocity of these head movements is proportional to their amplitude (Zangemeister *et al.*, 1981). Head movements are considerably slower than saccades and continue after fast eye movements have brought the target onto the fovea. Gaze direction, defined as the sum of eye position in the orbit and head position in space, is stabilized by the generation of smooth eye movements in the opposite direction to head movement. These smooth

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eye movements drive the eyes from the eccentric orbital position achieved by the saccade back towards the midorbital position as the head aligns with the target (Bizzi *et al.*, 1972; Zangemeister and Stark, 1981). The compensatory smooth eye movements (CEMs) are normally generated by the vestibulo-ocular reflex (VOR) (Bizzi *et al.*, 1971) but on occasion may be preprogrammed (Kasai and Zee, 1978; Zangemeister and Stark, 1981).

During pursuit, the head provides a platform from which smooth eye movements are generated (Gresty and Leech, 1977). Head motion causes vestibular smooth eye movements in the opposite direction, which drives the eye off target. Thus the VOR must be cancelled in order to maintain the target on the fovea during head-free pursuit (Lanman *et al.*, 1978).

Patients with Parkinson's disease have impaired saccadic initiation and accuracy, low smooth pursuit velocities, hypoactive VOR and impaired visual suppression of the VOR (White *et al.*, 1983*a*, *b*). Kennard *et al.* (1982) found that parkinsonian patients tend to avoid head movements during gaze shifts. When instructed to move their heads, the initiation of head motion is usually delayed until after onset of saccade. Our study was designed to analyse ocular motor function during rapid gaze shifts and during pursuit with the head free to move.

## METHODS AND SUBJECTS

Six patients with idiopathic Parkinson's disease and 1 with posthypoxic parkinsonism, all of whom participated in previous oculomotor investigations with the head fixed (White *et al*, 1983*a*, *b*), were studied. Criteria for clinical assessment have been published previously. Briefly, tremor, rigidity and bradykinesia were graded from zero (absent) to 3 (severe). A score of 2 or more for each of two signs, or a score of 2 for one sign in addition to a duration of disease greater than 5 yrs, was sufficient to classify a patient as having advanced disease. All patients were fully mobile and independent Four patients had advanced and 3 mild disease (Table 1), according to these criteria. The mean age of the patients was 56 yrs (range 39–74); 5 were men. Their results were compared with those of 5

TABLE 1 PATIENT INFORMATION

| *Case* | *Age yrs* | *Sex* | *Severity* | *Therapy* |
|---|---|---|---|---|
| 2 | 58 | F | Advanced | L-DOPA<br>trihexiphenidyl |
| 3 | 63 | M | Advanced | L-DOPA<br>benztropine mesylate<br>amantidine |
| 4 | 52 | F | Advanced | Trihexiphenidyl<br>amantidine |
| 6 | 75 | M | Advanced | None |
| 7 | 39 | M | Mild | L-DOPA<br>benztropine mesylate |
| 11 | 67 | M | Mild | L-DOPA |
| 12 | 44 | M | Mild | None |

Case numbers identify patients who participated in the previous studies of head-fixed oculomotor control (White *et al*, 1983*a*, *b*) normal subjects (mean age 51 yrs; range 42–65; 3 men). All subjects had the protocols fully explained to them and gave informed consent. No patients were demented as determined by neuropsychological criteria.

Horizontal eye movements were recorded by infrared reflection oculography and d.c. electro-oculography (EOG) simultaneously, as previously described (White *et al.*, 1983*a*). EOG was used to measure eye movements beyond the linear range of the infrared system (±20°) Head movements were recorded using a lightweight helmet connected to a precision quality potentiometer by a torsionally rigid cable. All data were stored on magnetic tape for off-line digitization The full system frequency response was 0–100 Hz after digitization

Compensatory eye movement (CEM) gain (the ratio of smooth eye movement velocity to head velocity) during active head movements was compared to the VOR gain (the ratio of vestibular smooth eye movement velocity to whole body rotational velocity) recorded during passive whole body rotation in darkness in the same patients (White *et al.*, 1983*a*)

Targets for gaze shifts were light-emitting diodes arrayed on a stimulus arc. The head-free pursuit target was a rear-projected laser reflected from computer-controlled, galvanometer-mounted mirrors (Sharpe *et al.*, 1979). All tests were performed first without and then with instructions for subjects to move their heads.

### *Saccadic gaze shifts*

*Predictable target steps.* The target was stepped from 30° left to 30° right at predictable intervals greater than 2 s. Responses to at least 40 target steps were analysed for each subject.

*Unpredictable amplitude target steps.* The target was stepped 5°, 10°, 15°, 20°, 40° or 60° to the left or right at predictable intervals (3 s) with direction amplitude varied pseudorandomly. The largest amplitude steps were centre-crossing. Responses to more than 100 target steps were examined for each subject.

### *Head-free pursuit*

*Ramp targets.* The target moved predictably at constant velocities of 10°, 20° or 40°/s from 10° left to 10° right, with 3 s intervals between ramps. Twenty-five ramps in each direction, at each velocity, were analysed for each subject.

*Sinusoidal targets.* Smooth pursuit of sinusoidally moving targets was measured at frequencies of 0 25, 0.5 and 1.0 Hz with peak-to-peak amplitude of 20°. We analysed 25 half-sinusoids at each frequency for each subject.

Data editing and analyses were carried out with a PDP 11/23 computer using interactive programs as previously described (White *et al*, 1983*a, b*). Significance of results was evaluated by using the Mann-Whitney U test.

## RESULTS

It was a striking finding that none of the patients chose to move their heads unless continuously encouraged to do so, regardless of the amplitude or velocity of the target movement. There was no difference in results between the patient with posthypoxic parkinsonism and patients with idiopathic disease. Normal subjects moved their heads through varying amplitudes under the same circumstances, without instruction. With instruction they made full amplitude head movements with each gaze shift. Thus all data reported here refer to protocols in which the subjects were instructed to move their heads.

### *Saccadic gaze shifts*

*Normal subjects.* Two patterns of eye-head coordination were observed. When target steps were predictable, the eye and head movement usually started almost simultaneously towards the target; mean latency for both was similar (Table 2). Head movements sometimes preceded eye movements. Once target foveation had been achieved by the saccadic eye movement, a CEM stabilized gaze position in space while the head continued to move (fig. 1A).

TABLE 2. EYE AND HEAD MOVEMENT LATENCIES (MS ± 1SD) FOR PREDICTABLE AND UNPREDICTABLE AMPLITUDE TARGET SHIFTS

| | *Eye* | *Head* |
|---|---|---|
| Predictable target steps | | |
| Normals | 260 ± 60 | 280 ± 50 |
| Patients | 350 ± 140 | 380 ± 90 |
| Unpredictable amplitude target steps | | |
| Normals | 270 ± 40 | 330 ± 40 |
| Patients | 310 ± 140 | 430 ± 120 |

When the amplitude and direction of target steps were unpredictable, normal subjects still attempted to anticipate target shifts, but less frequently. Eye movements (mean latency 270 ms) led head movements in these normal subjects by 60 ms on average (Table 2). Again, CEMs were generated with the eyes returning towards the primary orbital position as the head moved. The end point of saccades made when the head was moving was difficult to judge due to the flattening of the eye position trace. We used the point when eye movement velocity, obtained from the computer differentiation of the position trace, returned to zero, to determine termination of the saccade and thus measure saccade amplitude.

Head movement amplitudes varied at each target amplitude despite encouragement to generate head movements actively. Target shifts of 60° were used for the predictable amplitude and direction protocol, thus generating the largest amount of data at a single amplitude. For these target shifts, the mean amplitude of head movement was 37° (SD 13°). Peak head velocity increased with increased amplitude of head movement (fig. 3C).

*Patients.* Saccadic gaze shifts were frequently composed of small slow head movements having gradual onsets and terminations. Patients most frequently attained the targets by using multiple hypometric saccades (fig. 1C, D, E, fig. 2B). When the target shifts were predictable, eye and head movements tended to coincide, both at prolonged latencies (eye 350 ± 140 ms; head 380 ± 90 ms; Table 2; fig. 1B). When target movements were unpredictable in amplitude and direction, saccades led head movement by an average of 120 ms, again at prolonged latencies compared with normals (Table 2). Saccade latencies were similar to those recorded in these patients with their heads fixed (330 ± 85 ms). These differences were not statistically significant when the whole patient group was compared with normal subjects; however, patients with advanced disease had the longest saccadic latencies

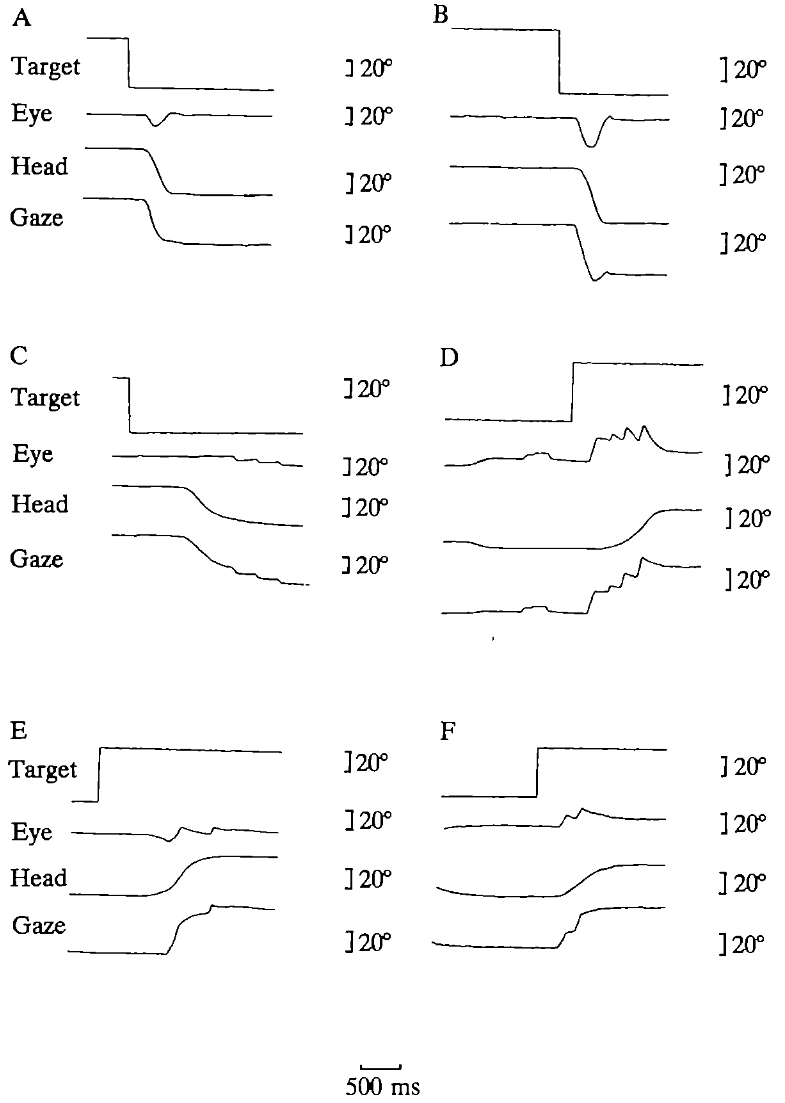

FIG. 1 Examples of head-free gaze shifts to targets predictable in amplitude, direction and timing A, normal subject. B, mildly affected patient: note the high gain CEM and small corrective saccade. C, severely affected patient· multiple hypometric saccades take the eye to the target Head movement occurs in the absence of CEMs and is responsible for gaze shift. D, severely affected patient: note the high gain CEMs, in both the eye and gaze traces, taking the eye off target and necessitating corrective saccades. E, severely affected patient. hypometric saccades and low velocity head movement F, normal subject: this exhibits a reduced VOR gain during the final stage of a large gaze shift so that gaze shift is completed by head movement alone. Upward deflections signify rightward eye, head and target movements.

and frequently made no head movement at all, despite forceful encouragement and despite the fact that they had not foveated the target.

The small slow head movements made by patients were too variable in amplitude for calculation of significant differences in peak velocity/amplitude relationships

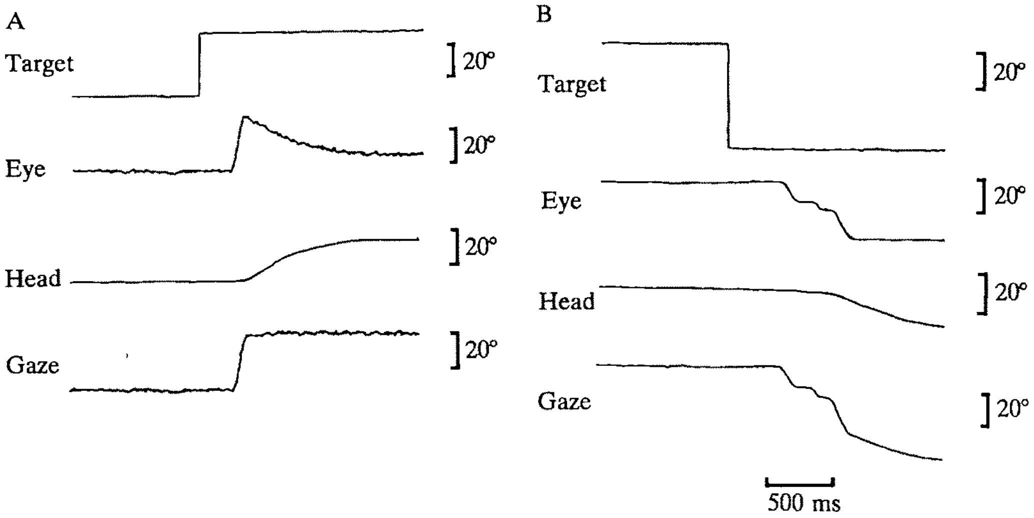

FIG 2 Examples of head-free gaze shifts to targets moving pseudorandomly in direction and amplitude A, normal subject. B, patient with advanced disease. Note the long latency to head movement by comparison with normal subjects. No compensatory eye movements are generated and a large part of the patient's gaze shift is achieved by the head movement alone

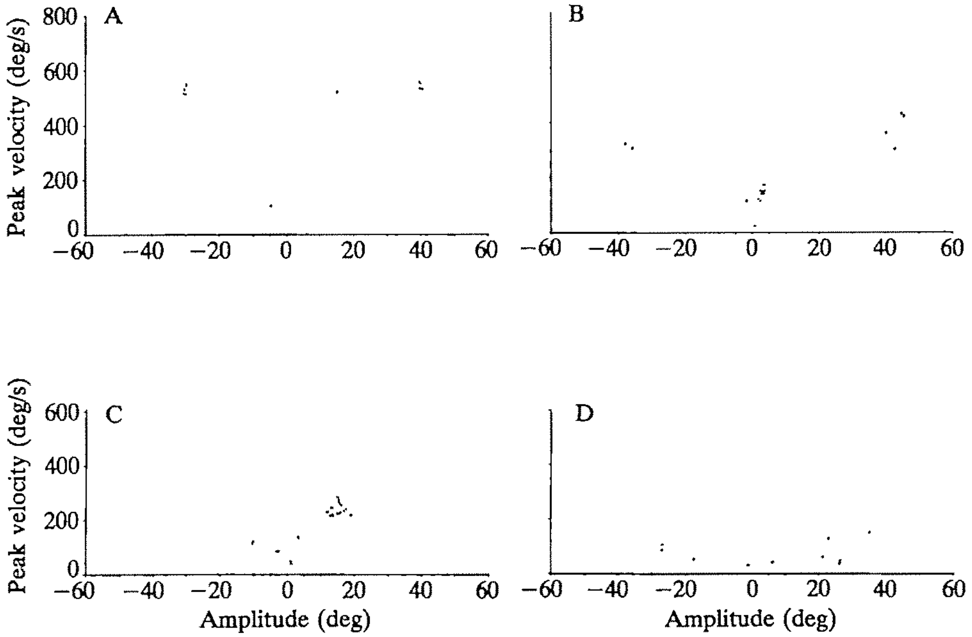

FIG. 3. Velocity versus amplitude plots of A, normal subject, eye movements; B, *Case 2* (advanced disease), eye movements; C, normal subject (from A), head movements; and D, *Case 2* (advanced disease), head movements Eye movements are saccades linked with head movements for 40° predictable target steps. A normal subject makes many saccades near full amplitude with smaller corrective saccades. A patient makes many hypometric saccades. The amplitude of both the normal subject's and the patient's head movements vary markedly, but generally the patient's head movements are slower for a given amplitude of head movement The asymmetry of saccadic function was not mirrored in general somatic function which was symmetrically impaired. Positive amplitude indicates rightward movements, and negative, leftward

compared with normal subjects. Patients were able to generate head movements with metrics comparable to those of normal subjects but made a greater number of slow movements than normal subjects (fig. 3C, D). Saccadic peak velocities for matched amplitudes were lowered in patients but, like normals, there was no significant difference whether the head was fixed or free (Table 4; fig. 3A, B). Gaze velocities were not compared. The variability of saccade amplitude, in association with head movement, resulted in a very small sample of gaze shifts of amplitudes which could be compared with those of normals.

Between these hypometric saccades, patients generated smooth eye movements (fig. 1D) resembling the compensatory smooth eye movements that stabilize gaze in normal subjects. In our patients, the gain of these CEMs (the ratio of smooth eye movement velocity to head velocity) varied from near zero (fig. 1C, E) to greater than unity (fig. 1D). For example, in fig. 1E, after an initial hypometric saccade which failed to reach the target, a low gain CEM was generated during head movement. Thus final attainment of the target depended almost entirely on the head movement. Such behaviour was rarely observed with normals and then only during the largest amplitude gaze shifts (fig. 1F).

### *Head-free smooth pursuit*

The gain of head-free pursuit was measured as the ratio of gaze velocity (eye velocity plus head velocity) to target velocity. Gaze pursuit gain was not significantly different from pursuit gain measured previously with the head fixed (White *et al.*, 1983*b*), although mean gain at the lower sinusoidal target frequencies was lower than that of normals (Table 3). Normal subjects pursued ramp targets, with near unity gain, at ramp speeds up to 20 deg/s and sinusoidal targets at up to 0.5 Hz. Beyond these limits, pursuit gain deteriorated (Table 3; figs 4A, 5A, 6A). Patients made fewer smooth gaze pursuit movements, and at lower gain, for ramp targets at 10 and 20 deg/s (see fig. 6A, B), and had reduced pursuit gain during sinusoidal pursuit at all frequencies (Table 3).

With these targets, whether ramp (constant velocity) or sinusoidal, normal subjects tended to move their heads through the same or larger amplitudes than the target; thus the direction of image slip on the retina was occasionally reversed (figs 4A, 5A). Patients' head movements were more variable in amplitude and range than those of normal subjects. Even when head movement alone was inadequate to pursue the target, patients sometimes made smooth eye movements opposite to the direction of head movement. Such eye movements were counter-productive and rendered gaze pursuit even less accurate (fig. 5B).

Cases 3 and 7 were able to generate smooth eye movements during head-fixed protocols but were unable to pursue with the head free (Table 3). Both patients had impaired visual suppression of the VOR despite hypoactivity of the reflex in darkness and despite relatively preserved ocular smooth pursuit. They moved their heads minimally despite instruction and their results were not included in statistical analyses. On occasion, when they did move their heads, they were unable to pursue

TABLE 3 VOR GAIN DURING WHOLE BODY OSCILLATION*

| | *Frequency* (Hz) | *VOR gain darkness* | *VOR gain suppression* | *Frequency* (Hz) | *Pursuit gain (sinusoids) (head fixed)* | *Pursuit gain (sinusoids) (head free)* |
|---|---|---|---|---|---|---|
| Normals | | | | | | |
| | 0.3 | 0.68±0.16 | 0.09±0.08 | 0.25 | 0.92±0.07 | 0.80±0.09 |
| | 0.5 | 0.76±0.19 | 0.13±0.10 | 0.5 | 0.90±0.10 | 0.77±0.11 |
| | 1.0 | 0.97±0.13 | 0.35±0.16 | 1.0 | 0.55±0.12 | 0.55±0.13 |
| Patients | | | | | | |
| 1 | 0.3 | 0.31 | 0.30 | 0.25 | NR | 0.75 |
| | 0.5 | 0.62 | NR | 0.5 | NR | 0.5 |
| | 1.0 | 0.78 | 0.44 | 1.0 | NR | 0.36 |
| 2 | 0.3 | 0.06 | 0.13 | 0.25 | 0.88 | NR |
| | 0.5 | 0.03 | 0.06 | 0.5 | 0.79 | NR |
| | 1.0 | 0.18 | 0.38 | 1.0 | 0.50 | NR |
| 3 | 0.3 | 0.53 | 0.12 | 0.25 | 0.55 | 0.55 |
| | 0.5 | 0.51 | 0.29 | 0.5 | 0.45 | 0.53 |
| | 1.0 | 0.48 | 0.54 | 1.0 | NR | 0.47 |
| 4 | 0.3 | 0.04 | 0.45 | 0.25 | 0.63 | 0.62 |
| | 0.5 | 0.07 | 0.62 | 0.5 | 0.62 | 0.62 |
| | 1.0 | 0.72 | 0.98 | 1.0 | NR | 0.47 |
| 5 | 0.3 | 0.06 | 0.51 | 0.25 | 0.76 | NR |
| | 0.5 | 0.08 | 0.57 | 0.5 | 0.60 | NR |
| | 1.0 | 0.61 | 0.71 | 1.0 | 0.45 | NR |
| 6 | 0.3 | 0.91 | 0.24 | 0.25 | 0.88 | 0.74 |
| | 0.5 | 0.92 | 0.35 | 0.5 | 0.80 | 0.61 |
| | 1.0 | 0.90 | 0.43 | 1.0 | 0.49 | 0.29 |
| 7 | 0.3 | 0.75 | 0.18 | 0.25 | 0.85 | 0.83 |
| | 0.5 | 0.65 | 0.27 | 0.5 | 0.83 | 0.63 |
| | 1.0 | 1.10 | 0.82 | 1.0 | 0.48 | 0.38 |

Measured in darkness and during visual suppression, and of gaze pursuit gains with the head fixed and free Values are mean gain ± 1 SD NR = not recordable

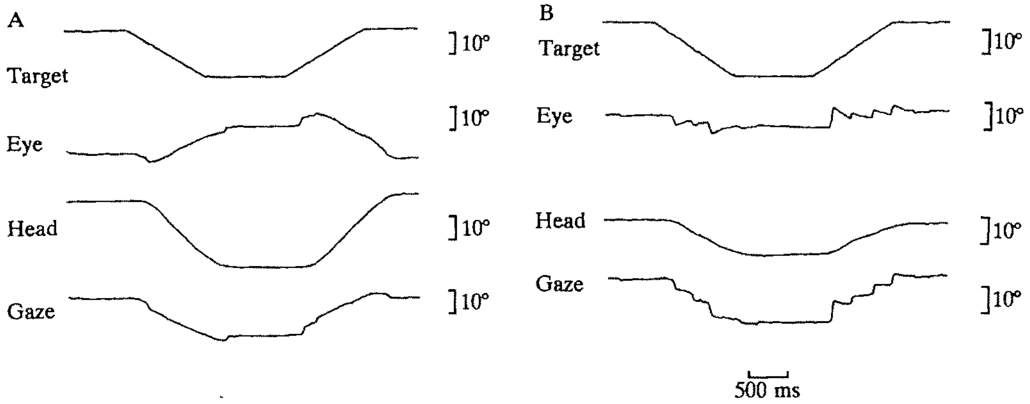

FIG 4 Examples of smooth gaze pursuit following 20 deg/s ramp targets. A, normal subject and B, patient with advanced disease. The normal subject has made smooth head movements which exceed the amplitude of target shift. He has generated vestibular smooth eye movements in the opposite direction to maintain fixation of the target as evidenced by the gaze channel which is the sum of eye and head position Only occasional small corrective saccades are required The patient has considerably less head movement and is unable to suppress his VOR. The smooth eye movements seen take the eye off target necessitating frequent corrective saccades. Upward deviation indicates rightward movement, and down, leftward.

TABLE 4 SACCADIC PEAK VELOCITIES (IN DEG/s ± 1SD) FOR SACCADES OF SELECTED AMPLITUDES

| | *Head free* | | |
|---|---|---|---|
| Saccadic amplitude | 4° | 10° | 18° |
| Normals | 157±37 | 286±83 | 375±79 |
| Patients | 140±34 | 248±65 | 291±119 |
| | *Head fixed* | | |
| Normals | 176±15 | 314±43 | 396±54 |
| Patients | 142±37 | 256±65 | 341±83 |

the target and were unable to regain fixation as long as the target continued to move, even if they ceased head movement.

Most patients showed similar pursuit gain values whether the head was fixed or free. However, Case 2, who had advanced disease and severe impairment of all eye movements with the head fixed, retained some capacity to suppress her VOR gain at higher frequencies of passive oscillation. This patient was unable to pursue a sinusoidal target at any frequency with the head fixed but, with her head free, she pursued targets smoothly, albeit at lower gain than for normals (Table 3). With the head free, all but one patient with mild disease (Case 12) had gaze pursuit gains lower than normal at all frequencies of sinusoidal target movement (Table 3). For ramp targets, patients' normalized pursuit duration (summed duration of all pursuit movements divided by the summed duration of all target movements) was lower than normals. Furthermore, mean pursuit velocity was lowered at all ramp velocities (fig. 6A, B).

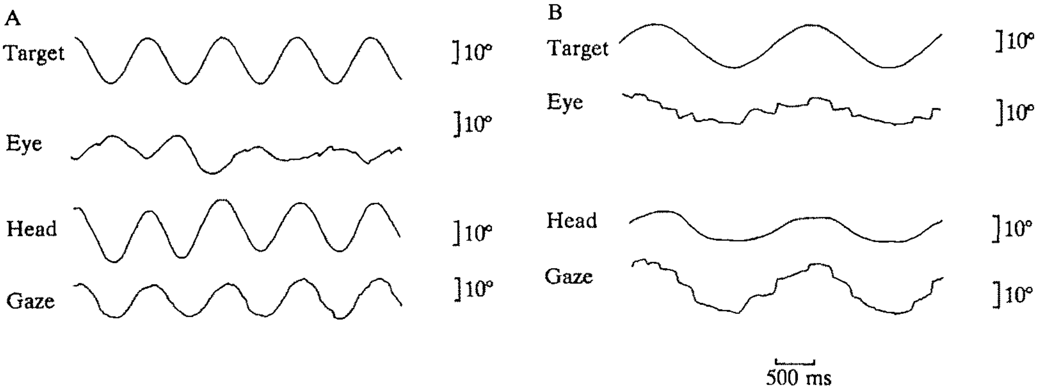

FIG 5. Examples of smooth gaze pursuit of sinusoidal targets at 0 5 Hz for normal subjects (A) and at 0 3 Hz for a patient (B) with advanced disease The normal subject makes large amplitude head movements requiring smooth vestibular eye movements in the opposite direction to track the target accurately The patient was unable to track a target at 0 5 Hz and at 0 3 Hz, pursuit was achieved by a combination of small amplitude head movement and frequent corrective saccades Occasional smooth eye movements are seen opposing head movement These may be generated by the VOR. Upward deviation indicates rightward movement

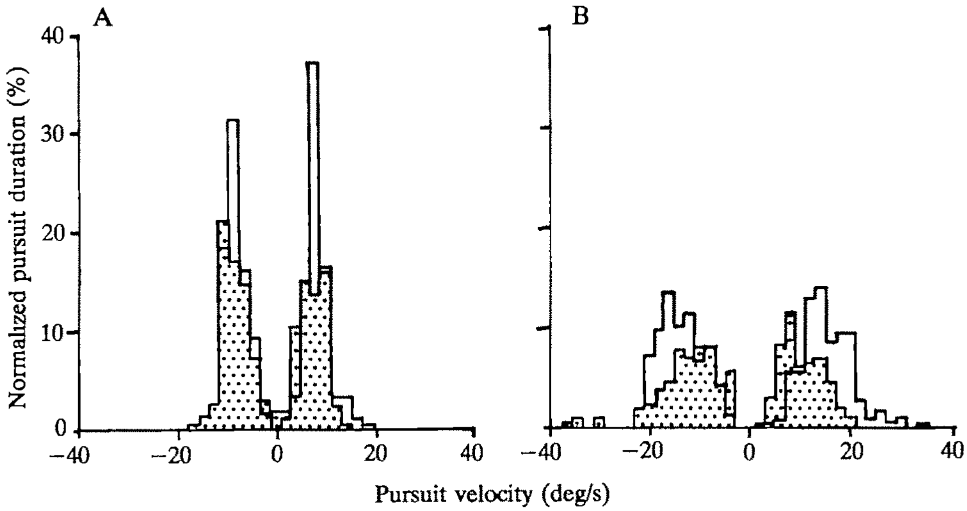

FIG. 6 Histograms of normalized smooth gaze pursuit duration (cumulative duration of smooth gaze movements at a specific velocity expressed as a percentage of the cumulative ramp duration) while tracking predictable target ramps, for a patient with advanced disease (dotted area) and a normal subject (open area) A, 10 deg/s ramps and B, 20 deg/s ramps Note that the patient spends less time tracking at velocities near that of the target. Positive velocity indicates rightward tracking.

Cases 11 and 12 pursued targets better with their heads fixed than free. The mean pursuit gain for Case 12 was only minimally lowered but he made fewer pursuit movements with the head fixed than free (Table 3).

## DISCUSSION

We have detected abnormalities of eye-head coordination not previously reported in Parkinson's disease. Normal subjects preferentially use saccades alone to achieve gaze shifts less than 20°. For larger gaze shifts, they initiate saccades towards the target and move their heads towards the new direction of gaze. Following the saccade, CEMs oppose head movement and stabilize gaze direction (Zangemeister and Stark, 1982*a*).

Shimizu *et al.* (1981) reported that parkinsonian patients, unlike control subjects, preferred to move their heads during head-free gaze shifts of 30° and were able to stabilize gaze direction in space. They assumed the VOR was normal and noted that saccades, although hypometric, had normal velocities. However, they did not report the relationship of velocity to amplitude. They concluded that eye-head coordination was normal in parkinsonism. Kennard *et al.* (1982) noted that patients preferred not to move their heads. Saccadic latencies were reported as normal but head movement latency was prolonged. Their patients generated CEMs opposed to head movement but sometimes preprogrammed opposing eye movements preceding the head movement.

In the experimental situation, expectations of performance may result in alteration of the normal response. For this reason we standardized the instructions to all subjects and studied a range of gaze shift amplitudes and conditions. Differences between our study and those reported above may be attributable to differences in the severity of parkinsonism or the experimental protocols. From our observations, parkinsonian patients rarely move their heads spontaneously, and then only for the largest gaze shifts. Most patients exhibited prolonged eye and head movement latencies for all paradigms. Saccades during head movements were slow and hypometric, and smooth gaze pursuit gain was lowered. CEMs frequently had abnormal gain, ranging from zero to greater than unity, and resulted in gaze inaccuracy. Occasionally smooth eye movements preceded head movement.

### *Saccadic gaze shifts*

*Latencies*. Normal subjects' eye and head movement latencies vary with the experimental paradigm, and are affected by neurological disease (Zangemeister and Stark, 1982*b*). For predictable target shifts, head movement latency can be reduced, coinciding with eye movement onset (Zangemeister and Stark, 1982*a, b*). We observed similar behaviour in our subjects.

The mean latencies of our patients' eye and head saccades were prolonged for both predictable and unpredictable gaze shifts (Table 2). The differences were not statistically significant but the longest latencies occurred in patients with severe disease. Despite instruction and encouragement, patients at all stages of disease frequently failed to make head movements or moved so slowly that precise determination on onset and offset was impossible. The necessary exclusion of these trials from statistical analysis biases mean latencies towards normal.

*Velocity*. The mean peak velocity of head-free eye saccades was lower, although not significantly, in all normal subjects than those of a similar amplitude made with the head fixed. Although patients can make saccades having normal peak velocity/amplitude relationships (Table 4), they make more slow saccades than normals.

Morasso *et al.* (1973) noted reduction of eye saccadic velocity during head movements made by monkeys, and attributed this to addition of the opposed VOR. Rapid head movements, made by our subjects, might slow saccades by activating vestibular smooth eye movements but, in our patients, the observed slowing of saccades during head movement was not significant (Table 4). Furthermore, patients with advanced parkinsonism actually had hypoactive VOR activity measured during passive whole body oscillation in darkness (White *et al.*, 1983*a*). Opposing vestibular CEMs seem unlikely to reduce saccadic velocities appreciably.

Patients frequently, and normal subjects occasionally, made gaze shifts during which target foveation was achieved by head movement alone after the eyes ceased moving. Tomlinson and Bahra (1986*b*), in monkeys, and Laurutis and Robinson (1986), in humans, have demonstrated that the VOR is not subtracted from saccades during gaze shifts greater than 20°. In monkeys, the VOR is active during gaze shifts less than 20°. Tomlinson and Bahra (1986*a, b*) suggested that a separate motor program was operative for large gaze shifts in monkeys and that the eye movements were analogous to vestibular quick phases which are slower than saccades of matched amplitude (Jurgens *et al.*, 1981*b*). Laurutis and Robinson (1986) proposed that feedback of an efference copy of the gaze signal slowed the eye movements in their subjects.

In the cat there appear to be two gaze mechanisms. Stimulation of the anterior superior colliculus evokes retinotopically-coded saccades with variable small head movements (Guitton *et al.*, 1980). Stimulation of the intermediate zone resulted in saccades to an orbital location associated with invariable, short-latency head movements during which the VOR was cancelled and gaze was the sum of the evoked saccade and head movement alone (Roucoux *et al.*, 1980).

Our observations suggest that our patients frequently used a phylogenetically older motor program, akin to that used by afoveate animals, wherein the fast eye movements are analogous to the quick phases of vestibular nystagmus. Such a paradigm is used by normal subjects only for large gaze shifts.

*Compensatory smooth eye movements.* CEMs during saccadic gaze shifts are thought to be vestibular in origin (Bizzi *et al.*, 1971, 1972; Zangemeister and Stark, 1981, 1982*b*), but may be preprogrammed in labyrinthine-defective humans and monkeys (Bizzi *et al.*, 1972; Kasai and Zee, 1978) and in normal humans (Roucoux *et al.*, 1981). Our patients sometimes generate CEMs with low gain, but often with normal or high gain, despite a hypoactive VOR. Gain variation was vastly more variable than VOR gain, even in the same patient.

CEMs may be vestibular, preprogrammed or adapted cervico-ocular reflex movements, as observed in labyrinthine defective humans and monkeys (Kasai and Zee, 1978; Dichgans *et al.*, 1973). In those studies, the cervico-ocular reflex did not fully compensate for an absent VOR, and preprogrammed CEMs were implicated. Preprogrammed CEMs did not seem to be an adaptive response to hypoactive vestibular eye movements in our patients, as the variation in CEM gain often produced gaze inaccuracy. Low gain CEMs may be explained by the hypoactive VOR observed in advanced disease (White *et al.*, 1983*a*). However, patients with mild disease had normal VOR gains measured in darkness. Thus the low gain of CEMs during active head movement in our patients would indicate that they were preprogrammed.

It appears that our patients' program selection for small and large gaze shifts was frequently inappropriate and integration of motor activity with sensory (vestibular) information was impaired. Such disturbances indicate degeneration of higher executive functions in the saccadic gaze system.

### *Head-free pursuit*

Normal subjects, during head-free pursuit, often moved their heads faster and further than the target. The VOR was appropriately suppressed and gaze pursuit gain was equivalent to the gain of head-fixed ocular pursuit. Gresty and Leech

(1977) suggested that head movements increase the effective ocular motor range but do not enhance pursuit performance otherwise.

In Parkinson's disease, head-free pursuit gain is similar to that measured with the head fixed (White *et al.*, 1983*b*). When free to move their heads, patients, like normals, prefer to pursue with their eyes alone for the amplitude of target movement we have tested. When instructed to move their heads in pursuit of the targets, patients, unlike normals, chose not to move their heads most of the time. Gaze pursuit (the sum of eye movement and head movement) was predominantly saccadic in all patients.

The anatomical substrates for these deficits of the saccadic and smooth pursuit systems are uncertain. Schiller *et al.* (1980) demonstrated in monkeys that combined lesions of the frontal eye fields and the superior colliculus produced slowed hypometric saccades. The caudate nucleus sends axons to the medialis dorsalis and ventralis anterior nuclei of the thalamus which, in turn, project to prefrontal cortex and frontal eye fields (Alexander *et al.*, 1986). Brinkman and Porter (1979) identified cells in the supplementary motor cortex of monkeys which activated with ipsilateral eye movements and which Schlag and Schlag-Rey (1985) showed to fire before gaze shifts, whether the monkey's head was fixed or free. This region is probably influenced by basal ganglia outflow. Striatal efferents also influence nigrotectal pathways (Jayaraman *et al.*, 1977; Hikosaka and Wurtz, 1983). Further studies have demonstrated that the substantia nigra pars reticulata inhibits neurons of the superior colliculus (Hikosaka and Wurtz, 1985*a, b*) and could thereby affect saccade and gaze saccade generation.

Ablation of the superior colliculus in cats impairs the VOR and its modulation for 3 to 4 weeks (Flandrin and Jeannerod, 1981). Boussaoud and Joseph (1985) injected the GABA agonist muscimol into the substantia nigra pars reticulata, which projects to the superior colliculus, thus reducing VOR gain for ipsilateral rotations. It seems that nigrocollicular pathways influence the VOR, although, the duration of effect of a fixed lesion is not certain. Parkinsonism may permanently disrupt these circuits.

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# SPATIAL FREQUENCY-DEPENDENT ABNORMALITIES OF THE PATTERN ELECTRORETINOGRAM AND VISUAL EVOKED POTENTIALS IN A PARKINSONIAN MONKEY MODEL

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## SUMMARY

The pattern visual evoked potential (PVEP) and pattern electroretinogram (PERG) were studied in 5 cynomolgus monkeys before and during the development of a parkinsonian syndrome induced by MPTP. The stimuli were vertical bars of four spatial frequencies (0.5, 1.2, 2.5 and 3.5 cycles/degree (cpd) modulated at temporal rates of 1, 4, 6, and 8 Hz. Following MPTP administration, all monkeys developed parkinsonian signs accompanied by changes in the amplitude and latency of the PVEP and PERG. Sinemet L-dopa/carbidopa administration produced temporary recovery of both PVEP and PERG. Two of the monkeys were followed for a prolonged period 30–40 days after MPTP, the parkinsonian signs showed partial recovery; the PVEP latency and amplitude to 2.5 and 3.5 cpd stimuli and the latency to 1.2 cpd showed improvement but remained abnormal. The latencies of PERGs were normal, but the amplitudes were significantly reduced when stimuli of 2.5 and 3.5 cpd were used. Both PVEP and PERG to 0.5 cpd stimuli returned to normal. No further modifications were seen in the recordings performed 6 months and 1 year later. This study demonstrates (1) that spatial frequency-dependent electrophysiological abnormalities occur in the MPTP-treated monkey, a result previously found in human Parkinson's disease, and (2) that dopamine has a specific function in neurotransmission in the visual system of primates

## INTRODUCTION

Systems other than the nigrostriatal pathways are affected in Parkinson's disease (PD). Kuhl *et al.* (1984), for instance, have described abnormal metabolic processes throughout the parkinsonian brain. Reduced olfactory acuity has also been related to loss of dopamine in the olfactory pathways (Ansari and Johnson, 1975). Many studies suggested that the visual system is affected in PD. The original description

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of delay in the pattern visual evoked potential (PVEP) (Bodis-Wollner and Yahr, 1978) had been confirmed by several authors (Delwaide *et al.*, 1980; Gawel *et al.*, 1981; Mintz *et al.*, 1981; Kupersmith *et al.*, 1982; Tartaglione *et al.*, 1984; Sollazzo, 1985; Nightingale *et al.*, 1986; Onofrj *et al.*, 1986*c*). Other investigators, however, reported that PVEP alterations were present in only a minority of patients (Regan and Neima, 1984) or that PVEP latencies were within normal limits in PD (Ehle *et al.*, 1982, Halliday, 1982; Hansch *et al.*, 1982; Dinner *et al.*, 1985). The characteristics of the stimuli used by these various authors may account for such differences in published results (Bodis-Wollner, 1985; Tartaglione *et al.*, 1985; Onofrj *et al.*, 1986*c*).

Several studies suggested that visual changes in PD are linked to a lack of dopamine (Bodis-Wollner and Yahr, 1978; Gawel *et al.*, 1981; Onofrj *et al.*, 1986*c*). The most likely site of this dopamine deficiency is the retina since the presence of retinal dopaminergic neurons in primates has been confirmed by several authors (Frederick *et al.*, 1982; Holmgren, 1982). Studies of the electroretinogram elicited by diffuse full-field flashes (flash ERG) have disclosed abnormalities in PD subjects (Iudice *et al.*, 1980; Gottlob *et al.*, 1987; Jaffe *et al.*, 1987), which would be consistent with an impairment of retinal function. Moreover, the pattern electroretinogram (PERG), which appears to arise from proximal retinal structures (Maffei and Florentini, 1981; Maffei *et al.*, 1985) is also abnormal in PD (Nightingale *et al.*, 1986; Gottlob *et al.*, 1987).

The intravenous administration of l-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) produces persistent and severe parkinsonism in humans (Davis *et al.*, 1979; Ballard *et al.*, 1985) and in monkeys (Burns *et al.*, 1983, Langston *et al.*, 1984), with the major signs (tremor, rigidity, and bradykinesia) being comparable to those present in advanced stages of idiopathic PD.

We studied the effects of MPTP administration on 5 cynomolgus monkeys. The PVEP and PERG were measured for different spatial and temporal frequencies. The aims of this study were to assess (1) if the PVEP and/or PERG were abnormal in MPTP-treated monkeys; (2) if these abnormalities were similar to those seen in PD patients; and (3) if Sinemet (L-DOPA with carbidopa) administration could influence the visual electrophysiological changes seen in the MPTP-treated monkeys.

Our findings show stimulus-specific dopamine-dependent abnormalities in both the PVEP and PERG in MPTP-treated monkeys, consistent with changes seen in human PD. In addition, we can offer a plausible explanation for the divergent results in the literature.

## METHODS

Five young cynomolgus monkeys (Macaca fascicularis) were the subjects of our study. For electrophysiological testing, the monkeys were lightly anaesthetized with Ketalar (4–6 mg/kg), and brought from the animal department to our laboratory. They were comfortably restrained in a primate chair with Velcro straps around the chest and the arms. In order to maintain head position, stainless bars mounted on the chair were connected to three bolts secured with acrylic cement on the skull of the animal during a previous surgical procedure (Glover *et al.*, 1986). When the animal was awake and alert, simultaneous PVEP and PERG were obtained by monocular stimulation. PVEPs were recorded either from screw electrodes previously implanted in the skull of 2 monkeys (Glover *et al.*, 1986) or using EEG needle electrodes inserted subcutaneously. We have previously found that no significant differences exist between the recordings obtained with the two kinds of electrodes in our laboratory (Ghilardi *et al.*, 1987). The active PVEP site was 1 cm above the inion on the midline and the reference site was at the vertex In 1 monkey we also recorded the responses from right and left lateral electrodes Since there was no difference between the responses recorded from the midline and lateral sites, both before and after MPTP, we will report the result from only the midline PVEP. PERGs were recorded in 1 monkey from miniature electrodes previously implanted in the orbital bone of both eyes (Glover *et al.*, 1986), and in the others from EEG needles inserted through the skin of the left and right lower lids. In all the monkeys, the active PERG electrode corresponded to the open eye, while the reference site corresponded to the opposite eye, which was patched with a white gauze pad. This eye patch was employed since it blurs spatial details with little attenuation of the mean light level. Another EEG electrode was inserted subcutaneously in the right mastoid area and served as the common ground.

After dark adaptation, pupillary diameter was 7 mm (which is normal for Macaca fascicularis in our laboratory) in both pre- and post-MPTP monkeys. The exception was 1 monkey (No. 2) which, after MPTP, developed a left miotic pupil, unresponsive to light (*see* below). During each testing session, the animal was constantly observed by one of the authors to ensure proper pattern fixation and to detect any signs of distress, somnolence, or eye movements. In addition, eye movements were measured with EEG needle electrodes inserted subcutaneously around the eyes (inferiorly, superiorly, and laterally) and monitored on a Tektronix type 532 oscilloscope. The data collection was interrupted and the data were discarded when the fixation was not considered satisfactory

A vertical grating with a square-wave luminance profile was presented in the counterphase and on/off modes. The stimulus was produced by projecting a 35 mm slide onto a mirror mounted on the armature of a galvanometer (Digitimer Ltd). The image was then projected onto a translucent screen which the monkey viewed This system allowed us to produce a large field (90 deg of visual angle), with mean luminance of 56 cd/m$^2$ and contrast of 90%. In order to compare our data with those previously reported in PD patients, four different spatial frequencies, 0.5, 1.2, 2 5 and 3.5 cycles/deg (cpd) were counterphase modulated at 1 Hz. In addition, in 2 monkeys, these same spatial frequencies were combined factorially with temporal frequencies of 4, 6, and 8 Hz, both in counterphase and on-off modulation The PERG and PVEP signals were amplified 20,000 times with filters settings of 0.3–100 Hz.

Between 256 and 512 responses to transient (i.e , 1 Hz) counterphase modulated stimuli were summated using an analysis time of 500 ms and viewed on a Nicolet 1070 averager and plotted by an X/Y plotter. Latency and amplitude of the transient PVEPs and PERGs were evaluated. Temporal modulation of the stimulus and data collection were controlled by a PDP 11/23 microcomputer. For steady-state conditions, the amplified PERG and PVEP signals were recorded in 2 s epochs, and analysed by the computer which has a capacity for artefact rejection. The accepted epochs of the steady state responses (i.e., 4, 6, 8 Hz) were subjected to Fourier analysis, where the bandwidth of each spectral component was 0.5 Hz. The amplitudes and phases of the first and second harmonics of the stimulus frequency were examined. Before MPTP administration, each monkey was tested at least 3 to 4 times for each stimulus condition.

After i m. injection of 5 mg/kg ketamine, 0.35 mg/kg free base MPTP was injected intravenously into the calf within 30 s, and then followed by 5 ml saline solution. Doses were delivered at 24 h intervals. Monkey 3 received a total of two doses, monkey 1, 4, and 5 a total of three doses and monkey 2 a total of four doses.

Using the procedure described above, electrophysiological recordings were performed from 10 to 30 days following the last MPTP injection in all monkeys, while 2 animals (Nos 1 and 3) were studied for a 1-year period. We also studied the acute effects of the administration of Sinemet® 110 (100 mg L-DOPA + 10 mg carbidopa). One tablet of Sinemet was pulverized, dissolved in water and then given to the monkey by nasogastric tube. The PERG and PVEP, as well as behavioural changes, were monitored for 6 h.

All procedures conformed to the ARVO Resolution on the Use of Animals in Research.

Student's t tests (two-tailed) for paired comparisons were performed on all data.

## RESULTS

### *PVEP and PERG before MPTP administration*

We obtained clear and reproduceable responses in all monkeys (fig. 1). The PVEPs obtained from our monkeys strongly resembled those recorded in humans. With counterphase transient stimulation, the PVEP waveshape consisted of a major positive peak occurring around 100 ms (P1), which was immediately preceded by a negative deflection at 65 to 75 ms (N1). Another negative component following the P1 (N2) had less a definite peak and latency (from 120 to 200 ms) and was variable between monkeys. We measured the latency of P1 and N1 and the amplitude of N1-P1 and P1-N2. For each spatial frequency, the latency of these two components did not vary by more than 8 ms in the same monkey, regardless of whether recordings were performed on the same day or were separated by days. However, the amplitude of the PVEP varied less than 20% in each monkey. Interocular differences were less than 4 ms for latency and 10% for amplitude in the 5 animals.

Transient PERGs were simultaneously recorded with the PVEPs. The waveform

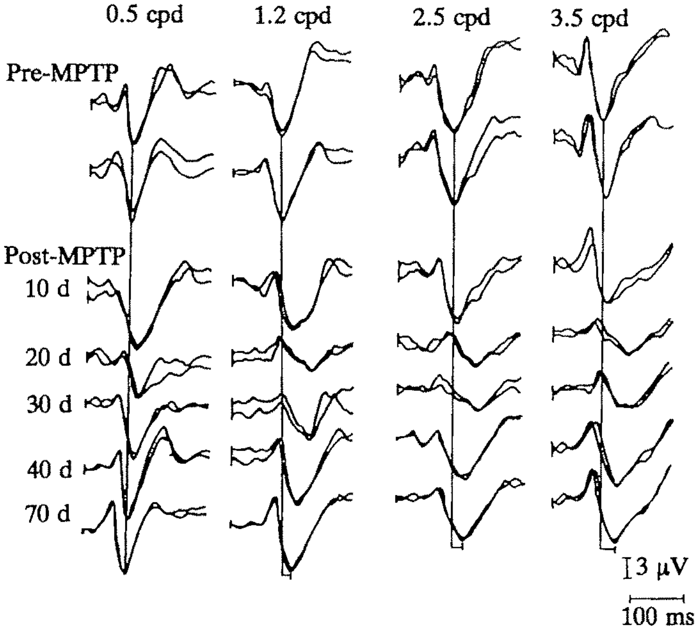

FIG. 1 PVEPs to 0.5, 1.2, 2.5, and 3.5 cpd stimuli, before and after MPTP administration in monkey 3, showing the stability and reproduceability of the responses in the same and different 'pre-MPTP' testing sessions Positivity is downwards and negativity upwards. Vertical lines indicate the normal latency of the major PVEP component, P1 Post-MPTP PVEP traces reveal a progressive delay and amplitude decrease in the first 20 days, while on day 30 no further worsening of the responses occurred. In this monkey, from days 30 to 40 a clear partial improvement is noticeable. No further changes were seen 70 days post-MPTP. Six months and 1 year later the PVEP had the same latency and amplitude (traces not shown). Notice that the effect of MPTP is dependent on spatial frequency, greatest for 3.5 cpd stimuli and minimal for 0.5 cpd

of the monkey PERG was similar to those seen in humans (fig. 2): a small negative deflection (a wave) occurring at 38 to 42 ms was followed by a stable positive deflection (b wave) around 52 to 64 ms. A negative peak which followed the b wave was not well defined and could vary in the same monkey in the same recording session by 20 ms or more. This component was not measured. The amplitude was measured from the peak of the a wave to the peak of the b wave. The normal range of variability of the a wave and b wave latencies in the same subject was 2 to 4 ms, while the a-b amplitude could vary by 10 to 25%. Interocular differences were less than 3 ms for latency and less than 10% for amplitude in all monkeys.

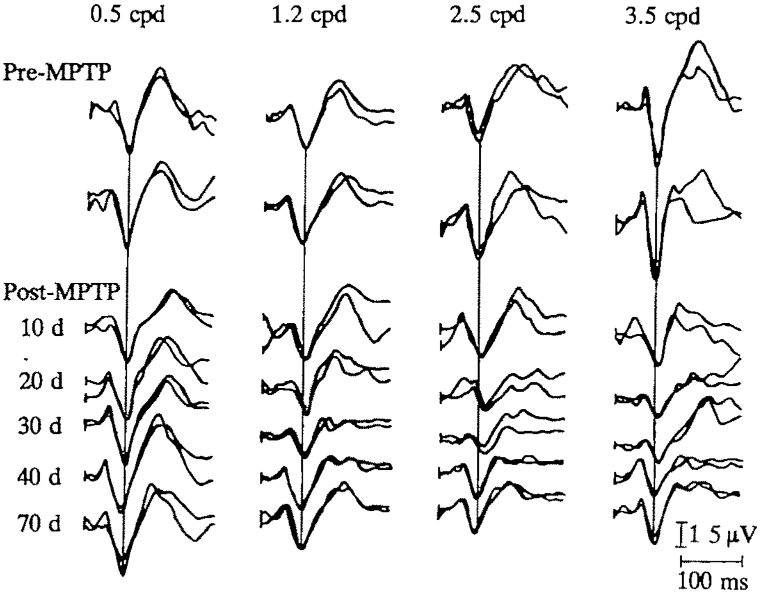

FIG. 2. PERGs recorded in monkey 3, before and after MPTP administration. The b wave is the major positivity (peak down) and the a wave the preceding negative peak (up). The latency and amplitude in the pre-MPTP recordings were replicable. The vertical lines indicate the normal latency of b wave. In the recordings of days 10 to 30 a delay in b wave latency and a marked reduction in amplitude is evident, while from day 40, only an amplitude decrement was seen for the PERG obtained with 2.1 and 3.5 cpd stimuli.

Steady-state stimulation yielded PVEPs with a quasisinusoidal waveshape. We analysed the amplitude and the phase of the harmonics of the temporal frequency of the stimulus (i.e., if stimulation frequency was 4 Hz, then the first harmonic was 4 Hz, the second harmonic 8 Hz, the third 12 Hz, etc.). The counterphase-modulated PVEP had the highest amplitude at the second harmonic frequency, while the on-off PVEP had the highest amplitude at the first harmonic. In the PERG the highest amplitude occurred at the second harmonic, either with counterphase or on-off modulation. No reliable first harmonic frequency component was detectable. In the same animal, for the same stimulus condition, the amplitude of the peak response could vary from 10 to 35%, while the phase oscillated by less than 30° in both PVEP and PERG. Interocular differences were less than 30° for phase and less than 10% for amplitude.

Since the interocular differences were negligible for all the measurements in the normal monkeys, we report the values obtained in one eye for each animal in Tables 1 and 2.

TABLE I MEAN VALUE OF P1 LATENCY (IN MS) AND N1-P1 AND P1-N2 AMPLITUDES (IN $\mu$V)*

| | *Before MPTP* | | | | *20 days after* | | | | *40 days after* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *cpd* | *0.5* | *1.2* | *2.5* | *3.5* | *0.5* | *1.2* | *2.5* | *3.5* | *0.5* | *1.2* | *2.5* | *3.5* |
| P1 latency | | | | | | | | | | | | |
| 1 | 97 | 112 | 121 | 124 | 110 | 156 | 156 | 161 | 101 | 134 | 144 | 152 |
| 2 | 91 | 95 | 104 | 105 | 108 | 147 | 161 | 172 | — | — | — | — |
| 3 | 90 | 94 | 104 | 107 | 112 | 142 | 160 | 170 | 99 | 112 | 132 | 150 |
| 4 | 94 | 102 | 110 | 118 | 111 | 150 | 160 | 167 | — | — | — | — |
| 5. | 93 | 101 | 110 | 113 | 110 | 148 | 161 | 168 | — | — | — | — |
| m(5) | 93 | 100 | 109 | 113 | 110 | 149 | 160 | 167 | — | — | — | — |
| m(2) | 93 | 103 | 112 | 115 | 111 | 149 | 158 | 165 | 100 | 123 | 138 | 151 |
| N1-P1 amplitude | | | | | | | | | | | | |
| 1 | 7.7 | 11.0 | 11.6 | 14.1 | 8.2 | 8.7 | 7.1 | 8.2 | 8.1 | 10.1 | 9.1 | 8.6 |
| 2 | 5.7 | 6.1 | 7.0 | 8.4 | 5.0 | 3.2 | 3.5 | 3.8 | — | — | — | — |
| 3 | 5.1 | 5.9 | 7.0 | 8.3 | 4.7 | 3.8 | 4.0 | 4.1 | 4.9 | 5.7 | 4.9 | 4.9 |
| 4 | 6.1 | 7.2 | 8.4 | 10.3 | 5.8 | 4.7 | 4.3 | 5.2 | — | — | — | — |
| 5 | 6.2 | 7.5 | 8.5 | 9.9 | 6.0 | 5.0 | 4.4 | 5.3 | — | — | — | — |
| m(5) | 6.1 | 7.6 | 8.5 | 10.2 | 5.9 | 5.1 | 4.7 | 5.3 | — | — | — | — |
| m(2) | 6.4 | 8.4 | 9.3 | 11.2 | 6.4 | 6.2 | 5.6 | 6.2 | 6.5 | 7.9 | 7.0 | 6.7 |
| P1–N2 amplitude | | | | | | | | | | | | |
| 1 | 8.7 | 14.8 | 16.2 | 16.8 | 9.0 | 8.1 | 7.2 | 7.8 | 8.6 | 14.0 | 9.1 | 9.4 |
| 2. | 8.8 | 9.4 | 9.2 | 12.1 | 5.4 | 4.8 | 4.1 | 4.0 | — | — | — | — |
| 3 | 8.7 | 9.6 | 9.6 | 11.0 | 6.3 | 4.7 | 4.3 | 4.5 | 8.7 | 8.9 | 6.7 | 6.0 |
| 4 | 8.2 | 11.2 | 11.6 | 13.1 | 5.8 | 5.2 | 5.3 | 5.0 | — | — | — | — |
| 5 | 8.0 | 9.8 | 10.8 | 13.0 | 6.4 | 4.9 | 5.7 | 5.8 | — | — | — | — |
| m(5) | 8.5 | 11.0 | 11.5 | 13.2 | 6.6 | 5.5 | 5.3 | 5.4 | — | — | — | — |
| m(2) | 8.7 | 12.2 | 12.9 | 13.9 | 7.6 | 6.4 | 5.7 | 6.1 | 8.6 | 11.4 | 7.9 | 7.7 |

* The values relate to 4 different spatial frequencies (0.5 cpd, 1.2 cpd, 2.5 cpd, 3.5 cpd) in 5 monkeys (Nos 1, 2, 3, 4, 5), before and 20 days after MPTP administration. In 2 animals (Nos 1, 3) the mean value of the PVEP recorded 40 days later is also given, m(5) indicates the mean value over all 5 monkeys and m(2) over 2 animals (Nos 1, 3)

### *Acute effect of MPTP: days 1 to 20*

Following MPTP administration, all monkeys developed parkinsonian signs. The appearance and severity of these signs were different for each animal. Bradykinesia, tremor and rigidity appeared from the third and ninth day after the first MPTP injection in the 5 monkeys. Other signs, such as a crouching position, frozen postures, impairment of the standing position, decrease of food intake, decreased vocalization, impaired eye movements, and increased salivation, were seen with different severity and time of onset in our animals. Details of the behavioural changes will be reported in a separate paper. In general, all monkeys showed a worsening of all signs in the first 30 days following the initial administration of MPTP, and tube feeding was required for 4 out of 5 monkeys during that period. It was necessary to tube-feed the fifth monkey (No. 1) for just the first 10 days. Three monkeys developed particularly severe parkinsonism: 2 of them (Nos 4 and

TABLE 2. MEAN VALUES OF THE b WAVE LATENCY (IN ms) AND a-b AMPLITUDE (IN $\mu$V) OF THE PERG

| | *Before MPTP* | | | | *20 days after* | | | | *40 days after* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *cpd* | *0.5* | *1.2* | *2.5* | *3.5* | *0.5* | *1.2* | *2.5* | *3.5* | *0.5* | *1.2* | *2.5* | *3.5* |
| b wave latency | | | | | | | | | | | | |
| 1 | 54 | 63 | 62 | 64 | 54 | 65 | 64 | 64 | 53 | 64 | 62 | 64 |
| 2 | 54 | 58 | 60 | 62 | 55 | 60 | 65 | 68 | — | — | — | — |
| 3 | 52 | 57 | 58 | 60 | 54 | 62 | 64 | 64 | 53 | 58 | 60 | 62 |
| 4 | 56 | 60 | 61 | 60 | 55 | 61 | 64 | 66 | — | — | — | — |
| 5 | 53 | 59 | 61 | 62 | 54 | 60 | 62 | 62 | — | — | — | — |
| m(5) | 54 | 59 | 60 | 62 | 54 | 62 | 64 | 65 | — | — | — | — |
| m(2) | 53 | 60 | 60 | 62 | 54 | 63 | 64 | 64 | 53 | 61 | 61 | 63 |
| a–b amplitude | | | | | | | | | | | | |
| 1 | 3.5 | 2.7 | 2.5 | 3.1 | 3.5 | 1.9 | 1.8 | 1.5 | 3.5 | 2.4 | 1.8 | 1.6 |
| 2 | 4.6 | 3.0 | 3.4 | 3.4 | 4.4 | 2.2 | 1.6 | 1.4 | — | — | — | — |
| 3 | 3.5 | 2.9 | 3.1 | 4.5 | 3.6 | 1.8 | 1.5 | 1.3 | 3.6 | 2.5 | 2.0 | 1.8 |
| 4 | 4.6 | 2.8 | 3.0 | 3.5 | 4.5 | 1.8 | 1.4 | 1.0 | — | — | — | — |
| 5 | 3.8 | 2.8 | 3.0 | 3.1 | 3.7 | 1.9 | 1.3 | 1.1 | — | — | — | — |
| m(5) | 4.0 | 2.8 | 3.0 | 3.5 | 3.9 | 1.9 | 1.5 | 1.3 | — | — | — | — |
| m(2) | 3.5 | 2.8 | 2.8 | 3.8 | 3.5 | 1.8 | 1.6 | 1.4 | 3.5 | 2.4 | 1.9 | 1.7 |

5) had received 3 MPTP doses, while the third (No. 2) had received 4 doses. This monkey (No. 2) also developed a left miotic pupil which was unresponsive to light and dark and was accompanied by mild ptosis. We could not record reliable responses by stimulating the left eye of this animal. Thus only responses from the right eye are reported and taken into account for statistical evaluation. One animal which received only 2 doses of MPTP (No. 3) initially showed signs with the same intensity as monkeys 4 and 5 but the progression was less severe.

Recordings performed on days 10, 15 and 20 post-MPTP showed the appearance and progression of electrophysiological abnormalities that paralleled the severity of the parkinsonian signs (Onofrj *et al.*, 1986*b*). The electrophysiological tests showed the highest degree of abnormality 15 to 20 days after MPTP administration. At that time, PVEPs were significantly delayed for all spatial frequencies ($P<0.001$). Since numerous statistical analyses were performed, in the interest of brevity and clarity the relevant t values have not been included. All t values will be provided on request. Table 1 and fig. 1 show that the greater delay occurred with increasing spatial frequency. The increase in mean PVEP latency of the 5 animals which occurred 20 days after MPTP treatment was 17 ms for 0.5 cpd stimuli, 49 ms for 1.2 cpd, 53 ms for 2.5 cpd, and 54 ms for 3.5 cpd (*see* Table 1). N1 latency was delayed similarly to P1. Both N1-P1 and P1-N2 amplitudes were significantly decreased with 1.2, 2.5, and 3.5 cpd stimuli ($P<0.01$). With the 0.5 cpd grating, only P1-N2 amplitude was significantly decreased ($P<0.01$), and on closer inspection of the data, this amplitude was abnormal in 3 out of 5 animals. In the 5 monkeys, the amplitude decrement was greater for the higher spatial frequencies.

For example, for the PVEP elicited by 1.2, 2.5, and 3.5 cpd stimuli, the mean N1-P1 amplitude measured 20 days post-MPTP was, respectively, 67%, 55%, and 52% of the baseline data (*see* Table 1: 5.1/7.6; 4.7/8.5; 5.3/10.2), while the amplitude of the PVEP to 0.5 cpd stimuli fluctuated within the normal range in all the monkeys. The P1-N2 amplitude decreased to 77%, 50%, 46%, and 41%, respectively, for stimuli of 0.5, 1.2, 2.5, and 3.5 cpd.

The major change in the post-MPTP PERG was a marked decrease in amplitude seen with 1.2, 2.5, and 3.5 cpd stimuli ($P<0.001$). At those spatial frequencies, a-b amplitude was abnormal in all monkeys. While the latency of the a wave did not change, irrespective of the spatial frequency of the stimulus, the b wave latency was delayed in 3 animals (monkeys 2, 3, 4) for 3.5 cpd stimuli and in 2 (Nos 2, 3) for 2.5 cpd stimulation. Only 1 monkey (No. 3) had an abnormal latency when a 1.2 cpd stimulus was used. These changes in b wave latency 'before MPTP' versus '20 days after' were statistically significant using stimuli of 1.2, 2.5, and 3.5 cpd ($P<0.05$). However, comparison of the 'before MPTP' and '20 days after' b wave latencies did not reach statistical significance for the 0.5 cpd spatial frequency. With the exception of monkey 3 (previously mentioned), no interocular differences were found in the other 4 monkeys.

### *Chronic effects of MPTP: from day 30*

In 2 monkeys (Nos 1, 3) we studied the evolution of both parkinsonian signs and electrophysiological abnormalities over a 1-year period. We saw a partial regression of all the parkinsonian signs and a complete disappearance of some of these signs, beginning 30 days after the last MPTP injection. At the sixtieth day, we saw no further improvement. At 1 year, the 2 monkeys were moderately bradykinetic and rigid with mild tremor and masked facies. Tube feeding was no longer necessary from 20–45 days after MPTP administration.

While the monkeys showed signs of behavioural recovery, the PVEP also improved both in latency and in amplitude. The first significant improvement appeared in the P1 latency to the 0.5 and 1.2 cpd stimuli on day 34: in both monkeys, the latency of P1 improved by 8 to 15 ms. In the same testing session, the PVEP amplitude increased by 10 to 30% for all spatial frequencies. The PERG amplitude increased by 20 to 40% for all spatial frequencies except 0.5 cpd. In monkey 3, b wave latency returned to the normal range. From 40 days onwards, the latency and amplitude of PVEP elicited by the 0.5 cpd stimulus fluctuated within the normal range in both monkeys. However, despite the initial improvement of 10 ms or more, an abnormal latency was constantly recorded in both animals when stimuli of 1.2, 2.5, and 3.5 cpd were used. These latencies were significantly delayed when compared with the 'pre-MPTP' values ($P<0.01$). Moreover, from Table 1, it is clear that the amount of the improvement in latency was related to the spatial frequency of stimulation: the lower the spatial frequency, the more complete was the latency recovery. In this chronic phase, the amplitudes of both N1-P1 and P1-N2 were within the normal range for 0.5 and 1.2 cpd, while only partial recovery occurred for the PVEP obtained with 2.5 and 3.5 cpd stimuli. These amplitudes also were still significantly different when compared with the pre-MPTP amplitudes ($P < 0.02$).

On day 40, the amplitude of the PERGs to the 1.2 cpd stimulus reached normal values. At the same time, the amplitudes of PERGs elicited by 2.5 and 3.5 cpd stimuli were still abnormal and significantly different from the baseline data ($P < 0.01$). However, b wave latency for all spatial frequencies was in the normal range and did not change significantly throughout the follow-up period. In summary, within 40 to 45 days, the latency and amplitude of both PERG and PVEP reached values which remained stable at the 1 year follow-up.

Forty-five and 60 days following the last MPTP injection, steady-state responses were recorded in the 2 monkeys. At that time, no significant changes in amplitude were seen for steady-state modulated responses, compared with the baseline pre-MPTP data. The 0.5 cpd grating evoked PVEPs with phase and amplitude values within the normal range. When stimuli of 1.2, 2.5, and 3.5 cpd were used, however, the second harmonic frequency component of PVEP elicited by counterphase modulation was significantly different from the baseline data. As shown in fig. 3, while a phase change of 40–60° occurred for 1.2, 2.5, and 3.5 cpd when 4 Hz modulation was employed, PVEP elicited by 3.5 and 2.1 CPD gratings fell 90–100° out of the normal range only when 6 and 8 Hz modulation was used. On-off modulation produced PVEPs which were 60–80° out of phase for 2.1 and 3.5 cpd at all temporal frequencies tested (4, 6, and 8 Hz). In addition, the phase of the

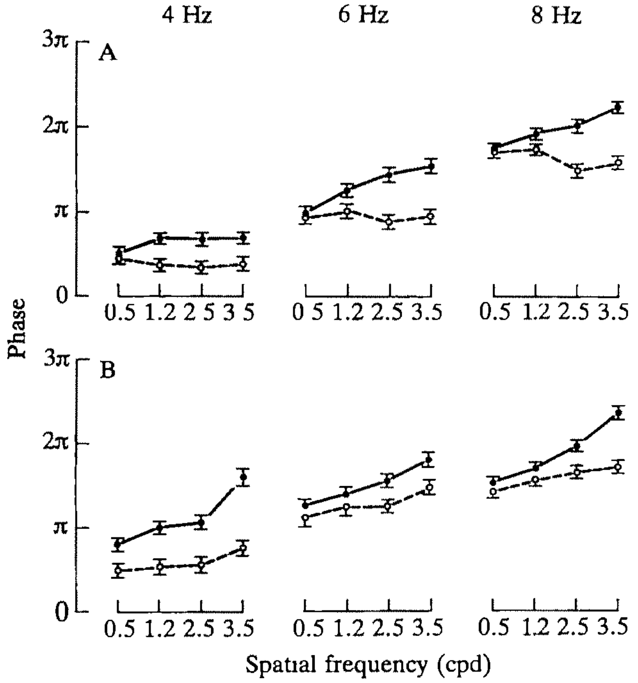

FIG 3 The phase of the steady-state PVEP before and after MPTP in monkey 1 is plotted. Each point represents the mean ± SEM of at least four recordings. Open circles and interrupted dashed lines represent the pre-MPTP results, while the solid circles represent the post-MPTP recordings. A shows the phase of the second harmonic of PVEP elicited by steady-state counterphase modulation as a function of the spatial frequency for the three temporal frequencies tested. For spatial frequencies of 2.5 and 3.5 cpd there is a constant phase lag for all temporal frequencies used (more pronounced for 6 and 8 Hz), for 1.2 cpd stimuli a clear difference is seen only using 4 Hz temporal modulation. The phase did not change when 0.5 cpd stimuli were used. B shows the phases of the first harmonic of PVEP obtained with on-off steady-state modulation as a function of the spatial frequency. The most significant phase delay occurred for 2.5 and 3.5 cpd at all temporal frequencies.

PVEP to the 0.5 cpd and 1.2 cpd stimuli was abnormal when 4 Hz, but not 6 or 8 Hz, was used.

Steady-state counterphase modulation produced PERGs which were 50–60° out of phase for 1.2, 2.1, and 3.5 cpd when 6 and 4 Hz were used. With 8 Hz, delayed phase (40°) was seen only for 2.1 and 3.5 cpd stimuli. The phase of the PERG to 0.5 cpd pattern was normal. With on-off modulation, all spatial frequencies, including 0.5 cpd, were similarly affected when 4 Hz was employed (40° delay); however, when 6 and 8 Hz were employed, PERG were 50–60° out of phase only for 2.1 and 3.5 cpd stimuli.

### *Acute effects of administration of L-DOPA on transient PVEP and PERG*

In the 2 monkeys in which we performed long-term follow-up recordings (Nos 1, 3), we also studied the acute effect of the administration of Sinemet on the PVEP and PERG. This study was accomplished on days 20 and 40 post-MPTP. On both occasions, 15 min after the administration of 1 Sinemet 110 via nasogastric tube, signs such as rigidity, bradykinesia and tremor completely disappeared. This improvement lasted about 6 h and was accompanied by changes in both PVEP and PERG.

Fig. 4 shows the progression of the PVEP changes to a 3.5 cpd stimulus over 3 h on day 20: the peak of the improvement both in amplitude and in latency was seen within 15 min and lasted for about 1 h. After that period, the PVEP gradually increased in latency; 2 h later, the PVEP decreased in amplitude. After 4 h, despite the presence of beneficial effects on behaviour, the PVEP had the same amplitude and latency as the baseline post-MPTP recordings. Since the greatest improvement

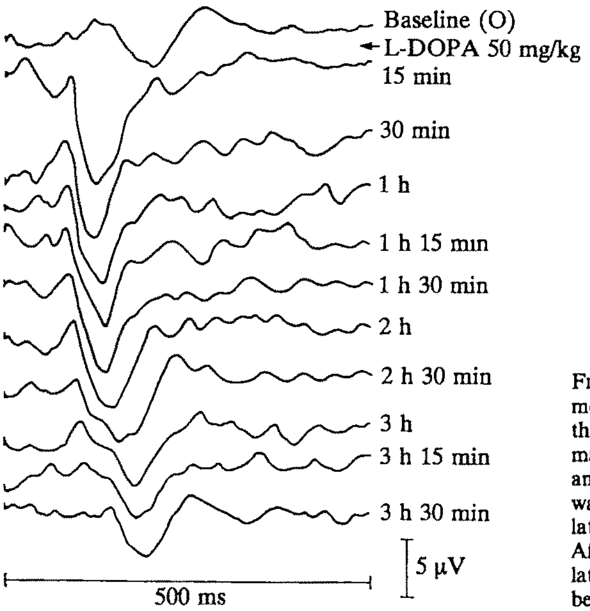

FIG. 4. Modification of PVEP to 3.5 cpd in monkey 3, 20 days post-MPTP, before and after the administration of Sinemet After 15 min the major positive and negative peaks increased in amplitude and shifted of 40 ms the improvement was still present 90 min later, but subsequently the latencies increased and the amplitudes decreased. After 4 h the PVEP had the same amplitude and latency of the pre-L-DOPA trace, while the behavioural changes were still present.

of the electrophysiological tests was seen from 15 to 75 min following drug administration, the results reported below were all collected during that period.

As shown in figs 5 and 6, the latency and amplitude of the PVEP and PERG improved following Sinemet administration. Once more, the effects were dependent on spatial frequency: the higher the spatial frequency, the greater the improvement. On day 20, Sinemet reduced PVEP latencies by 30 to 35 ms when 3.5 and 2.5 cpd stimuli were used and by 6 to 17 ms when 1.2 and 0.5 cpd were used. Despite these statistically significant decreases in latency ($P<0.02$), PVEP latencies did not improve to the normal range. Following Sinemet administration, the PVEP amplitudes significantly increased for all stimuli ($P<0.01$) and reached the normal range. The PERG was simultaneously recorded with the PVEP; PERG amplitude (in both animals) and latency (in monkey 3) also became normal for all spatial frequencies tested.

The same experiment was repeated on day 40. At that time, as described above, responses to the 0.5 cpd stimulus were normal without therapy, while to higher spatial frequencies both the PERG and PVEP were abnormal. Following Sinemet administration, however, the PVEP and PERG reached the normal range of amplitude and latency to all stimuli. The improvement was dependent on spatial frequency: in the 2 monkeys, the latencies of the PVEP decreased by 25 and 35 ms respectively for 3.5 cpd stimuli, by 18 and 24 ms for 2.5 cpd, and by 15 and 17 ms for 1.2 cpd. The amplitude increments for both PERG and PVEP were statistically significant when spatial frequencies of 3.5 and 2.5 cpd were used ($P<0.01$), while the changes of amplitude to 1.2 and 0.5 cpd stimuli failed to reach statistical significance. The most evident effect of Sinemet occurred with spatial frequencies nearer to the peak of the monkey's contrast sensitivity function (Miller *et al.*, 1980).

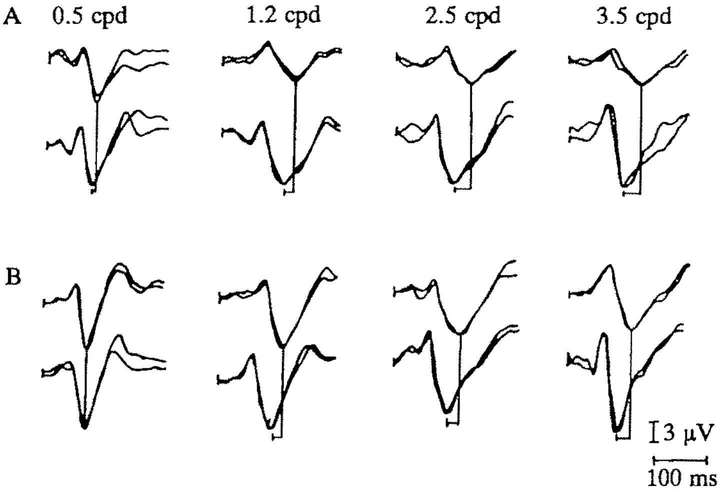

FIG. 5 Acute effect of the administration of Sinemet in monkey 3 showing the traces obtained for the four spatial frequencies tested The experiment was performed 20 (A) and 40 days (B) after last MPTP injection *Upper traces*, pre-Sinemet; *lower traces*, post-Sinemet. Partial recovery of PVEP latency is evident at day 20 and full recovery at day 40, reaching the range of the pre-MPTP recordings.

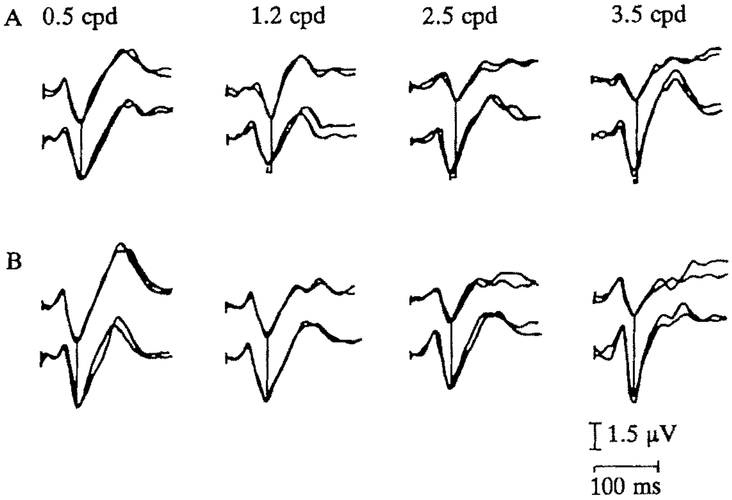

FIG. 6 PERG changes following Sinemet, A, 20 and B, 40 days post-MPTP. These traces were recorded simultaneously with the PVEP shown in fig. 5 The *upper traces* of the pairs are pre-Sinemet, the *lower traces*, post-Sinemet. For the PERG the recovery was complete in both recording sessions.

### *Problems in testing monkeys*

A criticism frequently raised in electrophysiological research is the degree of certainty that the pattern is focused on the monkey's retina. Since the monkey was secured in the primate chair by head screws, we ensured that the eye was directed toward the pattern. The animal was carefully observed by the examiner, and the recordings aborted when fixation was not considered satisfactory. However, it is likely that, from time to time, the animal may have directed its gaze away from the pattern or did not accommodate properly. The efficacy of our method of recording is attested by the fact that the PVEP and PERG traces could be replicated within the same and different testing sessions in these animals (*see* Results) and in others (Marx *et al.*, 1986*a, b*; Onofrj *et al.*, 1986*a, b*). Furthermore, in previous studies conducted in our laboratory (Marx *et al.*, 1986*b*; Siegel *et al.*, 1986), we demonstrated that PERG amplitude in the normal cynomolgus monkey decreases in a regular manner as a function of optically induced blur. Moreover, we have been able to record reliable and replicable PERGs and PVEPs in normal and aphakic monkey eyes which have been optically corrected, following refraction by cycloplegic retinoscopy. When these eyes were not optically corrected, it was not possible to record a PERG or PVEP that exceeded noise level, for all spatial frequencies of stimulation. Thus, since the responses can be attenuated or extinguished by refractive error, we consider that the animals in our studies were indeed looking at the pattern.

## DISCUSSION

Our data show that both PVEPs and PERGs are abnormal in the MPTP-treated monkey shortly after drug administration, and that abnormalities are still present in the chronic phase of MPTP-induced parkinsonism, although partially improved. All electrophysiological abnormalities were dependent on spatial frequency and reversible by dopamine precursor administration, confirming the results of previous PVEP studies in PD patients (Tartaglione *et al.*, 1985; Onofrj *et al.*, 1986*c*). The PERG abnormalities in our MPTP-treated monkeys consisted of a reduction in amplitude rather than delayed latency. Since acute improvement can be seen following administration of Sinemet in both MPTP-treated monkeys and in human PD, we attribute the observed electrophysiological changes to functional damage to a catecholaminergic, most probably dopaminergic, system in the visual pathways of parkinsonian primates.

Histological and neurochemical findings suggest that MPTP is selectively toxic to the pigmented dopaminergic neurons of the pars compacta of the substantia nigra of monkeys (Burns *et al.*, 1983, 1986), similar to what was seen in the first human case of MPTP intoxication (Davis *et al.*, 1979), and in 3 of our monkeys (Ghilardi *et al.*, 1986). Acute decreases in the levels of noradrenalin and dopamine levels in the cortex and striatum, accompanied by decreases of catecholamine metabolites in the cerebrospinal fluid, have been demonstrated in MPTP-treated monkeys; however, only dopamine levels remain depressed in the long term (Snyder and D'Amato, 1986). Thus the abnormalities seen in the acute phase must be related to à combined noradrenergic and dopaminergic deficiency, while the chronic phase abnormalities must relate to 'pure' dopaminergic deficiency. In fact our electrophysiological data do reveal significant differences between the 'acute' and 'chronic' stages.

Noradrenergic circuits have been described in the visual cortex of the Macaca fascicularis (Kosofsky *et al.*, 1984), and in the retina of several animal species (Hadjiconstantinou and Neff, 1984). In the visual cortex of the cynomolgus monkey, noradrenergic axons form two broad bands which extend through deep and superficial cortical layers (Kosofsky *et al.*, 1984). Since the PVEP probably reflects excitatory postsynaptic potential activity originating in the cortical layers (Mitzdorf, 1986), a noradrenergic deficit could underlie the PVEP abnormalities that we found in our monkeys immediately after MPTP administration. Possible contributions also may arise from the lateral geniculate nucleus (LGN) and retinal circuits. Although the role of noradrenalin in the LGN is not fully established, Andén *et al.* (1966) and Ungerstedt (1971) reported that the medial forebrain bundle of the noradrenergic system sends fibres to the LGN. However, the role of noradrenalin may be less specific. It is involved in the innervation of blood vessels (Hadjicostantinou and Neff, 1984). A transient noradrenergic deficiency could alter the retinal blood flow and cause a general impairment of PERG, regardless of the characteristics of stimulation.

In the 'acute' stage, the PVEPs were abnormal for all spatial frequencies, with the greatest abnormalities occurring with the highest spatial frequency used (3.5 cpd). PERG amplitude changes were also dependent on spatial frequency: while no amplitude reductions were seen for the 0.5 cpd grating, 32%, 50%, and 60% PERG amplitude reductions occurred using 1.2, 2.5, and 3.5 cpd stimuli, respectively. The PERG latency to spatial frequencies of 1.2 and above was delayed in 3 monkeys

(Nos 2, 3, 4), but normal in the other 2 animals. In addition, we found that both PERG and PVEP abnormalities were partially reversible by L-DOPA administration.

The spatial frequency dependence became more evident in the chronic phase of monkey parkinsonism, so that 40 days after MPTP, the PVEP was delayed only for spatial frequencies of 1.2 cpd and above, and the amount of PVEP delay increased with increasing spatial frequency. In addition, the PERG and PVEP amplitudes were abnormal only for 2.5 and 3.5 cpd. All these abnormalities were completely reversed following Sinemet administration. Moreover, spatial frequency-dependent phase delays were seen in the steady-state PERG and PVEP, regardless of whether counterphase or on-off modulation was employed. Thus these data suggest that a 'pure' dopaminergic deficiency does not affect visual responses below 1 cpd, a result consistent with studies performed in human PD patients (Bodis-Wollner and Yahr, 1978; Delwaide *et al.*, 1980; Gawel *et al.*, 1981; Mintz *et al.*, 1981; Kupersmith *et al.*, 1982; Tartaglione *et al.*, 1984; Regan and Neima, 1984; Sollazzo, 1985; Onofrj *et al.*, 1986*c*). The studies which did not detect abnormal responses in PD patients employed either flash stimuli (Yaar, 1980) or patterns of low spatial frequency (Ehle *et al.*, 1982; Dinners *et al.*, 1985), and some were performed during the effects of dopamine precursor treatment. By increasing the spatial frequency of stimulation, it is possible to increase the detection of abnormal PVEP in a human PD population (Onofrj *et al.*, 1986*c*).

We can exclude the possibility that our findings were due to a loss of the ability to focus, since we previously showed that the PERG and the PVEP in the monkey are differentially affected by dioptric blur (Marx *et al.*, 1986*b*). In addition, a loss of accommodative power due to MPTP seems doubtful, since both the PERG and PVEP reached the normal range of pre-MPTP values under Sinemet treatment. We are not aware of dopaminergic influences on the accommodation process. Since the PERG and PVEP to the lowest spatial frequencies are spared in both human PD and MPTP-induced parkinsonism, it appears that 'contrast', but not 'luminance' responses are affected in a hypodopaminergic state. By contrast responses, we refer to the responses obtained with spatial frequencies higher than 1 cpd, which arise for centre-surround antagonism (Enroth-Cugell and Robson, 1966). Alternatively, luminance responses (i.e., lower than 1 cpd) do not arise from spatial contrast mechanisms, but rather from changes in local luminance on the retina. However, we do not feel that the PERG and PVEP to the 0.5 cpd stimulus are pure luminance responses; instead, these responses must contain both luminance and contrast components, since both the PERG and PVEP to a 0.5 cpd grating can be changed by optically-induced blur (Marx *et al.*, 1986*b*; Siegel *et al.*, 1986), a result not possible in a pure luminance response. Thus we believe that in our monkeys, MPTP administration affected spatial contrast and, in turn, impaired the higher spatial frequencies to a greater degree.

The importance of spatial frequency has also been demonstrated by psychophysical studies in which specific losses in spatial contrast sensitivity have been observed near the peak of the curve (around 4 cpd) in PD patients (Domenici *et al.*, 1985; Bodis-Wollner *et al.*, 1987). Following dopaminergic therapy, an enhancement was seen in sensitivity to spatial frequencies around 3 to 5 cpd rather than to those around 0.5 to 1 cpd (Domenici *et al.*, 1985; Bodis-Wollner *et al.*, 1987). Thus both our data in the chronic parkinsonian monkey model and data in human PD emphasize the importance of stimulus size in testing the dopaminergic circuits of the primate visual pathways.

Our PERG results suggest that MPTP administration affects retinal circuitry. However, there is the possibility that MPTP may cause additional damage to other dopaminergic circuits in the visual pathways, since Martres *et al.* (1985) reported the presence of D2 receptors in layers V and VI of the visual cortex. Recently, Wong *et al.* (1985) have shown that a drastic reduction of b wave amplitude and an alteration in the oscillatory potentials occur in the flash ERG of rabbits studied soon after MPTP administration. These electrophysiological changes are accompanied by a decrease of the dopamine and DOPAC retinal levels and by a decreased fluorescence in retinal dopaminergic cells. Further support for our contention that our PERG results are due to an MPTP effect at the retinal level comes from a recent report by Porrino *et al.* (1987). Their data show an impairment of the metabolic activity in the striate cortex of MPTP-treated monkeys that can be reversed by L-DOPA administration; they propose that their results are due to a prechiasmatic dopaminergic deficit.

The importance of dopamine as a retinal transmitter has been reported by several authors in different animal species (Kramer, 1971; Dowling and Ehinger, 1975). Dopamine-containing interplexiform cells are in a position to provide feedback signals from the inner to the outer layers of the retina in several species, including man (Frederick *et al.*, 1982). A functional analysis of the role of dopamine in primate vision has not been reported; however, it is possible that it plays a major role in the shaping of spatial frequency sensitivity (Cohen and Dowling, 1983; Piccolino *et al.*, 1984; Teranishi *et al.*, 1984). Although we must be cautious about extrapolating data from single cell studies in nonprimates to our results in MPTP-treated monkeys, the spatial frequency specificity seen in our data seems consistent with this hypothesized role of dopamine in the retina. The finding of an abnormal PERG for the higher spatial frequencies confirms once more that there is an impairment of the retinal circuits involved in contrast detection. In fact, the most likely generators of the PERG in both subprimates and primates are the retinal ganglion cells, which are detectors of contrast rather than luminance (Maffei and Fiorentini, 1981; Maffei *et al.*, 1985). To our knowledge, only two reports are available about PERG in PD: in those studies (Nightingale *et al.*, 1986, Gottlob *et al.*, 1987), PERG amplitudes were reduced in the patients relative to the control observers.

In conclusion, we have shown that the MPTP-treated monkey provides a model for studying visual electrophysiological changes associated with dopamine deficiency. Our main findings are that PERG and PVEP abnormalities in the parkinsonian monkey model are (1) spatial frequency specific, and (2) related to a lack of dopamine, since these responses improved following Sinemet administration. These results are directly comparable to electrophysiological studies conducted in PD patients. We conclude that dopamine plays an important role in responses to patterned stimuli in the visual system of primates.

## ACKNOWLEDGEMENTS

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# SLOWLY PROGRESSIVE APHASIA IN THREE PATIENTS

## THE PROBLEM OF ACCOMPANYING NEUROPSYCHOLOGICAL DEFICIT

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## SUMMARY

Three patients are described presenting with a slowly progressive aphasic disorder associated with degenerative cortical disease. The symptoms began in the presenium and the length of illness was 4 to 5 years. The language disorder corresponded in all patients to a severe form of amnesic aphasia but a moderate to marked semantic breakdown was also found.

Formal language examination was complemented by extensive neuropsychological testing. This revealed a severe deficit in language-dependent cognitive tasks. The patients were given a follow-up language and neuropsychological examination. In addition to the deterioration of language functions, a significant decline was observed in nonverbal intelligence tasks even though their level of performance still remained within the normal range. Follow-up with standardized intelligence tests might detect a trend towards generalized dementia in similar cases. This would mean that these patients should be considered as presenting with slowly progressive aphasia preceding generalized dementia.

## INTRODUCTION

In 1982, Mesulam described 6 patients with a slowly progressing language disorder without associated intellectual or behavioural disturbances. The disorder was of insidious onset and led to gradual deterioration of language function, mostly in the form of severe anomic aphasia. CT scan studies suggested atrophy of the left perisylvian region. Mesulam concluded that these patients did not fit into conventional diagnostic categories such as Alzheimer's disease or Pick's disease because of the lack of additional disturbances of memory, intellectual function and behaviour. In most of these patients, symptoms began in the presenium. Mesulam pointed out that even in Pick's disease with predominant involvement of the temporal lobe, aphasia virtually never appears in isolation, but is embedded in a syndrome of personality and behavioural disorder. His patients had a history of up to 11 years and still presented exclusively with a language deficit without

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the emergence of additional features of dementia. The language production was characterized by anomia with long and frequent word-finding pauses. Mesulam did not reach a conclusive nosological diagnosis of the condition. He was not inclined to consider his cases as variants of Pick's disease because of the absence of an accompanying behavioural deficit.

In the same year Benson *et al.* (1982) described a series of patients who presented with quite similar neuropsychological problems. These patients did not have disturbances of memory or of spatial orientation. The authors regarded the neuropsychological condition as an 'angular gyrus syndrome simulating Alzheimer's disease'. The aetiology of the condition remained unresolved, although there was an implicit suggestion that vascular disease might be the underlying cause (p. 619).

During recent years, the existence and the nosological status of progressive yet restricted neuropsychological disturbances have been amply discussed in the literature. Many cases have been described where a language disturbance was the predominant or even the only presenting symptom (Foster and Chase, 1983; Heath *et al.*, 1983; Gordon and Selnes, 1984; Kirshner *et al.*, 1984; Pogacar and Williams, 1984; Assal *et al.*, 1985; Chawluk *et al.*, 1986). Other case descriptions focused on agnosic (Magnani *et al.*, 1982; De Renzi, 1986), apraxic (De Renzi, 1986) or spatial constructive disturbances (Crystal *et al.*, 1982; Cutler *et al.*, 1985). Nevertheless, the features and nature of a syndrome of slowly progressive neuropsychological impairment without generalized dementia have not been well delineated. We have observed 3 patients who appeared prototypical for a dissociated slowly progressive language impairment. Follow-up with extensive neuropsychological testing, however, also revealed a deterioration of nonverbal cognitive performance.

## CASE REPORTS

### *Case 1*

M.H., a 63-yr-old woman, was admitted in January 1983. The patient had been a successful and socially active business woman for several decades until four or five months before admission when she exhibited increasingly severe word-finding problems. On admission, she presented with the appearance and social behaviour of someone with an upper middle class background. There was no history of previous illness and, in particular, none of hypertension or minor cerebrovascular events. Neurological examination was negative Her blood pressure was 120/80.

Language behaviour was examined by the Aachen Aphasia Test (AAT) (Huber *et al*, 1983, 1984; a description of the test is given in Appendix 1). Spontaneous speech was characterized by very severe word-finding problems and periods of empty phrases There were some semantic, but only few phonemic paraphasias. Syntactic structure was complex. She often tried to overcome her word-finding problems by circumlocutions. These, however, were not always successful but instead produced new circumlocutions that led to frequent duplication and blending of elements as well as incomplete sentences. Nevertheless, the patient was able to discuss almost any kind of everyday problem and required only minimal support from the partner/examiner. The following (translated) example illustrates her spontaneous speech (for original transcript, *see* Appendix 3, 1).

It all started some time ago. There were some customers ... and then ... said ... asked .. I ..

> the girls ... (with a low voice) 'What's the name?' ... then could ... I have forgotten the name again ... they answered though ... then it was all right again

In the subtests of the AAT (Token Test, Repetition, Written Language, Naming, Comprehension) her language impairment was only moderate in degree. Standardized scores of the performance in the subtests are given, together with the results of the follow-up examination in fig. 1. The quality of errors, in particular in the naming task (including picture description), suggested the diagnosis of amnesic aphasia.

To attempt to detect further neuropsychological impairment, the patient was given the shortened version of the Leistungsprüfsystem (LPS-K), a battery of tests calling for a variety of psychological functions (Horn, 1983; Sturm and Willmes, 1983). This test is constructed according to Thurstone's Factors of Intelligence. It includes 3 verbal and 3 nonverbal subtests. A detailed description is given in Appendix 2. Again, standardized scores of the performance in the 6 subtests are given, together with the results of the follow-up examination (fig. 1)

Overall performance was average with respect to the normal population. Performance in language-dependent subtests was significantly inferior to that in visual perceptive and visual cognitive subtests. Performance in the nonverbal subtests of the LPS-K appeared to reflect her premorbid level of intelligence. In particular, she was good in recognizing rules and applying strategies.

The EEG was normal, as was Doppler ultrasonography of the extracranial arteries. A CT scan (fig. 4A), showed some cerebral atrophy and a slight degree of hypodensity of the cerebral white matter. Routine haematological and biochemical screening tests were negative.

Over the subsequent three years, language function deteriorated gradually, forcing the patient to abandon her printing business where she had to converse with the customers. Her social behaviour and emotional state remained unchanged. She was reported to lead an active social life She went to town on her own and attended social activities. She read the daily newspaper regularly and watched television with interest. Her friends became used to her word-finding problems and gained experience in adaptating to her impaired verbal communication.

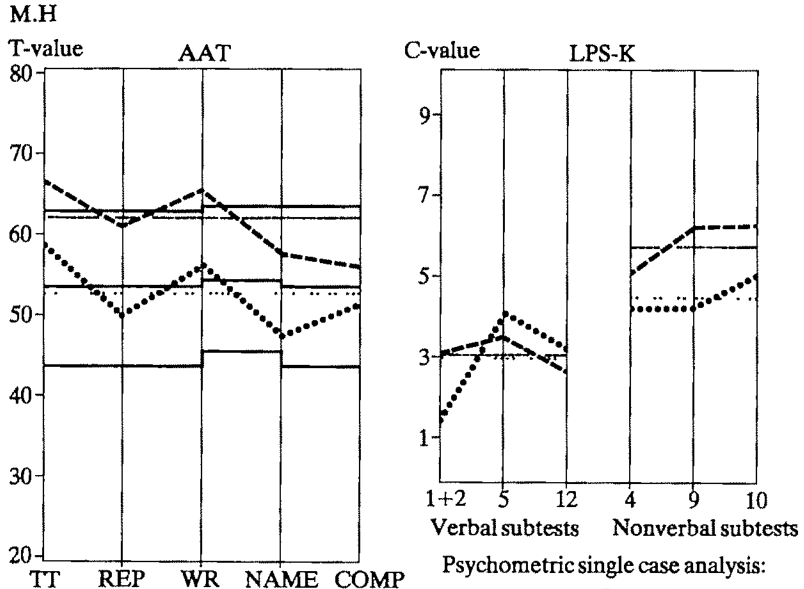
M.H. was seen again in March, 1986. She intimated that she was aware of a language handicap. When conversing, however, she made very few attempts at self-correction, even when her language output was severely paraphasic. She also did not understand a great many of the examiner's questions. Neurological examination remained entirely normal.

M.H. was again examined by means of the AAT. Spontaneous speech had deteriorated markedly. Her utterances consisted mainly of empty and stereotypic phrases. She rarely searched for missing words but instead filled the gaps with stereotypes. Only in a very global way did she manage to convey meaning The dialogue needed very strong support from the examiner. The following example illustrates her spontaneous speech (for original transcript, *see* Appendix 3, 2).

> Yes, three days ago (in fact, three years) and the beginning it was quite simple ... I could speak it exactly like that ... And I did not realize that I could ga ... go on, but Dr XY he noticed that I did not do the speaking very well and I also did receive something and then it was then shown that one takes this and that and all at once .. eh ... I know what that is ... Then I say ... but I cannot say it, and this . . this was the first ... that started ... and where I realized for myself that it was not correct ...

The qualitative analysis of expressive language in the subtests revealed the same features as recognized in spontaneous speech. Naming and descriptive naming yielded many semantically inadequate circumlocutions and paragrammatic errors. Naming of colours was surprisingly well preserved. In tasks such as repetition and reading aloud, the patient was conspicuous by phonemic uncertainties and lexical alterations. Writing was much more impaired than reading aloud. The errors consisted of perseveration and erroneous positioning of single letters. The level of test profile had deteriorated significantly (*see* fig. 1). On this occasion, Wernicke's aphasia was diagnosed.

The patient was again examined for neuropsychological deficit by means of the LPS-K and a test



| SPON | COM | ART | AUT | SEM | PHO | SYN |
|---|---|---|---|---|---|---|
| 1st ex | 3 | 5 | 3 | 3 | 4 | 4 |
| 2nd ex | 2 | 5 | 3 | 2 | 4 | 4 |

Psychometric single case analysis:

| | Comparison 1st | 2nd | z | P |
|---|---|---|---|---|
| Level of profile | 61 6 | 52 2 | 10 9 | <0 0001 |

Psychometric single case analysis:

| | Comparison 1st | 2nd | z | P |
|---|---|---|---|---|
| Level of entire profile | 4 03 | 3 42 | 2 41 | <0 008 |

| Comparison | Level of subprofiles | Comparison 1st | 2nd | z | P |
|---|---|---|---|---|---|
| Comparison | Verbal | 3 02 | 2 98 | 0 10 | 0 46 |
| | Nonverbal | 5 90 | 4 18 | 18 6 | <0 0001 |
| | z | −2 84 | −1 19 | | |
| | P | <0 0001 | <0 0007 | | |

FIG. 1. AAT and LPS-K profiles for *Case 1* The interrupted lines give the profiles and the corresponding overall levels of performance at the first examination (February 4, 1983) The dotted lines give profiles and levels at the follow-up examination (March 31, 1986).

AAT. The scores are given in standardized T-values referring to a sample of aphasic patients. The solid lines delimit from top to bottom four degrees of severity TT = Token Test, REP = Repetition, WR = Written Language, NAME = Confrontation Naming, COMP = Comprehension, SPON = Spontaneous Speech, COM = Communicative Behaviour, ART = Articulation and Prosody, AUT = Automatized Language, SEM = Semantic Structure, PHO = Phonologic Structure, SYN = Syntactic Structure

LPS-K. The scores are given in standardized C-values referring to a sample of normal subjects 1 + 2 = Vocabulary, 5 = Word Fluency, 12 = Recognition of Mutilated Words, 4 = Reasoning, 9 = Spatial Visualization, 10 = Flexibility of Visual Closure.

In the lower part of the figure the results of comparisons by means of single case analysis are shown From the AAT, comparison is made between the first and second examinations (Willmes, 1985) For the LPS-K, the entire profile of first and second examinations as well as performance in verbal and nonverbal subtests are compared (Sturm and Willmes, 1983).

for Verbal Learning and Memory. The LPS-K profiles of the two examinations were subjected to psychometric single case analysis (Huber, 1973). Performance profiles and the most important statistical data are given in fig. 1. In addition, M H. was given the performance subtests of the German version of the WAIS (Wechsler, 1964). She achieved a performance IQ of 107, indicating an average or even slightly above average test performance. She was unable to solve the verbal memory task and she was slightly impaired in Kimura's Recurring Figures Test (Hartje and Rixecker, 1978). She was unable to perform additions or subtractions even of two digit numbers and failed completely in multiplication and division (Basso and Capitani, 1979)

The patient did not have oral or limb apraxia (Lehmkuhl *et al*, 1983; Poeck, 1988) or ideational apraxia (Poeck and Lehmkuhl, 1980). Her performance in copying 11 geometric figures (De Renzi and Faglioni, 1967) was perfect. Her design of a house, a man, a bicycle and a car was good. In Raven's Progressive Matrices (Raven, 1938) her performance was within the normal range. She placed 9 cities correctly on a map showing the outline of the Federal Republic of Germany.

CT scan studies performed in September 1986 (fig. 4A) demonstrated left temporoparietal atrophy with enlargement of the insular cistern and atrophy of the convexity of the left temporal lobe. In addition, there was again some hypodensity in the hemisphere white matter. Yet unlike the situation in Binswanger's subcortical arteriosclerotic encephalopathy (Hacke *et al.*, 1982; Hassel *et al.*, 1986), evoked potential studies (VEP and SEP) were normal.

M.H. was also given a SPECT examination with intravenously injected 565 MBq$^{99m}$Tc Pertechnetat and 594 MBq$^{99m}$Tc-MPAO. There was a reduction in blood flow in the entire left hemisphere by an average of 13%. In the temporo-occipital region the reduction, compared with the right hemisphere, reached 20%. In the perisylvian region, there was a left/right difference of 15%. The volume SPECT showed a deficit of 17% in the left temporo-occipital area.

*Case 2*

H.S., a police officer, born June 20, 1929, was seen as outpatient in November 1985. He had been very successful in his career and his innovative energy was well recognized by his superiors. In 1976 he became chief of the local police department in a small town near Aachen. From 1979 he had held an administrative post of considerable responsibility.

In November 1982, his family noted some forgetfulness and word-finding problems, but he still managed to undertake his job until the beginning of 1985. Yet he maintained his social contacts, did various household repairs as well as gardening activities, and drove his car without any indication of spatial disorientation. He was a well-behaved man with perfect social manners. He assessed the situation well and was cooperative. His past medical history was unremarkable.

Neurological and general examination was negative, his blood pressure was 120/80. A CT scan performed in September 1986, showed a slight overall reduction of brain volume with selective atrophy of the temporal convexities and enlarged sylvian fissures. There were no vascular lesions.

H.S. was examined with the AAT. In spontaneous speech he was quite verbose. When conversing about everyday topics he easily made himself understood and managed to circumvent his word-finding problems. When pressed for more details, his utterances contained many linguistic stereotypes and preformed sentences. He often repeated the examiner's question in an echolalic way. At the syntactic level there were some blendings and reduplications of parts of the phrases. Many phrases were incomplete because of word-finding difficulties. These features were less conspicuous when the linguistic situation allowed for a higher degree of freedom. Speech production was well articulated and prosody was good. Oral language was accompanied and sometimes accentuated by appropriate gesticulations.

The following is an excerpt of the first interview (for original transcript, *see* Appendix 3, 3).

> Q: Would you please let me know first how your problems started?
>
> A: Yes, how did it start? It was like this, eh, let's say, I don't know it very precisely, you understand. It could be that 2 or 3 years ago, eh, well, wait a minute, when I had been on duty for 30 years, uh, well, then I was permitted to go to a sanatorium Well, and, uh, now it is like this. Up to this moment I used to smoke, uh, 30 cigarettes every day, yes. Then I went to a sanatorium where the doctor said it would make sense that I quit smoking, no, and the .. I was in that sanatorium with a friend of mine, actually a relative, and this man did not smoke, and, then during the time in the sanatorium, uh, uh, then I managed to loose weight, 6 kg, and then I came back and stopped smoking. And that is now, and in particular before I was 50, uh, and since that time, now I am

56, Uh, uh, since that time I have never smoked, and that is not bad either. Well, I have saved roughly 14000 DM, anyhow.
Q: You have made a precise calculation?
A: Yes, 30 cigarettes per day, you know, and, uh, then I came back from the sanatorium and then I have ... of the 6 kg ... 5 kg, uh, a little more eaten, as a surrogate, well, I am 184 cm tall.

In the Token Test the patient obtained a percentile rank of 81 indicating a slight impairment. Repetition was good with a percentile rank (PR) of 99. Written language was equally good (PR = 93), Naming was particularly good (PR = 37), and Comprehension was impaired to a moderate degree (PR = 59). Examples of responses in the naming subtest (for original transcript, *see* Appendix 3, 4) were as follows.

Suitcase: Where I can put something in, what I have to take with me.
Broom: For sweeping.
Candle: Well, for example at Christmas, we need these.
Excavator: Well, it is not exactly a car, no, we don't drive a thing like that, farmers use it.
Vacuum cleaner: Well, is that for vacuuming ... a cleaning machine, isn't it?
Refrigerator: A small cupboard with something in it.
Helicopter: A flyer
Screwdriver: Well, I know exactly what I have to do with that.

Performance in the AAT examination indicated a language disorder of medium severity with prevalence of a semantic disturbance (*see* fig. 2). Syndrome classification was amnesic aphasia even though comprehension was impaired more than usually expected in this syndrome.

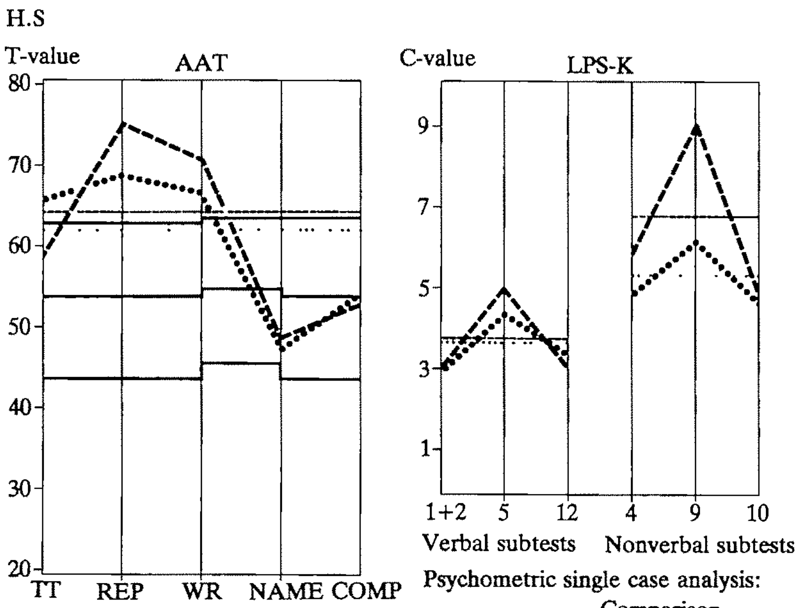
H.S. had an extensive neuropsychological examination by means of the LPS-K, a verbal learning and memory task (learning of word pair associations), with the Buschke Selective Reminding Test and the Recurring Figures Test of Kimura in the standardized German version In the LPS-K he obtained a standard IQ of 102, slightly below expected performance for his schooling and professional career.

An analysis with the planned linear contrast procedure introduced by Huber (1973) demonstrated that the difference between verbal and nonverbal tasks was highly significant, the verbal performance being extremely low (*see* fig. 2). A similar discrepancy was found for verbal and nonverbal memory performances. The patient was not able to memorize even 1 of 15 simple word pair associations. By means of the Buschke Selective Reminding Test it became evident that the patient had considerable problems both in storing and in retrieving linguistic information. In contrast, his memory performance in the Recurring Figures Test of Kimura was still average (standard value of 94).

H.S. was again examined in August 1986, four years after the onset of his memory and language problems. Neurological and CT findings were identical to those of the first examination. The patient was again quite logorrhoeic. The following is an example of his spontaneous speech (for original transcript, *see* Appendix 3, 5).

Q: Tell me what have you done during the last 6 months?
A: That is like this, I went to Dr W , uh, well I am with him all the time, no, and he has written a letter to the hospital that I should come to the outpatient clinic (in fact, it was the other way round). Well, then I have taken drugs, have brought them with me, uh, I tell you every drug I have taken, yes, yes, there was no improvement, you understand If you read now, well, and now it is like this, and so many words, you don't know any more what they are, you understand? But if I had the opportunity, supposing I read, well, a piece, no, if there were 10 words that one does not know any more, what is that, well, now I would precisely check and I would that, and probably I would have that, well, then I would rather read.

In the Token Test he reached a PR of 93, in Repetition of 96, in Written Language of 95, in



| SPON | COM | ART | AUT | SEM | PHO | SYN |
|---|---|---|---|---|---|---|
| 1st ex | 4 | 5 | 3 | 3 | 5 | 4 |
| 2nd ex | 3 | 5 | 3 | 3 | 5 | 4 |

Psychometric single case analysis:

|  | Comparison |  |  |  |
|---|---|---|---|---|
|  | 1 | 2 | z | *P* |
| Level of profile | 63 9 | 61 7 | 2 5 | <0 0062 |

Psychometric single case analysis:

|  | Comparison |  |  |  |
|---|---|---|---|---|
| Level of | 1st | 2nd | z | *P* |
| entire profile | 4 91 | 4 36 | 2 16 | <0 015 |

| Level of subprofiles | Comparison |  |  |  |
|---|---|---|---|---|
|  | 1st | 2nd | z | *P* |
| Comparison Verbal | 3 81 | 3 76 | 0 16 | 0 44 |
| Nonverbal | 6 87 | 5 42 | 16 06 | <0 0001 |
| z | −3 06 | −1 66 |  |  |
| *P* | <0 0001 | <0 0001 |  |  |

FIG 2. AAT and LPS-K profiles for *Case 2* For details, *see* legend to fig 1 1st examination: November 29, 1985, 2nd examination· August 27, 1986.

Naming of 34 and in Comprehension of 61. The severity of his language disorder had deteriorated slightly but significantly (*see* fig. 2). Syndrome classification remained unchanged.

H.S. was again given an extensive neuropsychological examination. We used a parallel form of LPS-K, the subtests Picture Arrangement and Block Test from the German version of the WAIS, the Recurring Figures Test and the 2 verbal Memory Tasks (*see* above). In the LPS-K he obtained a percentile rank of 42 corresponding to an IQ of 97. Planned linear contrast of the test profile demonstrated a considerably lower performance in the 3 language dependent subtests as opposed to the 3 (non or) relatively little language dependent subtests (*see* fig. 2). In Picture Arrangement he obtained only 4 points, which is clearly a subnormal performance. He was, in fact, able to solve only the most simple tasks. In the Block Test he solved all tasks swiftly and efficiently after some initial hesitation, and his performance was at the upper limit of the average performance (11 points). In the 2 verbal memory tasks he failed completely In the Recurring Figures Test he obtained a PR of only 5, in contrast to a PR of 27 six months before.

Performance on additional neurospychological investigations, including a test for acalculia (99/101) and the Progressive Matrices (49/60), was excellent. There was neither oral nor limb apraxia and no constructional apraxia.

A repeat CT scan performed in September 1986 (fig. 4B) revealed progression of the hemisphere atrophy which was particularly marked in the temporal lobes. This time there was a slight asymmetry, the left temporal lobe being more affected.

*Case 3*

M.W., born March 5, 1936, was first examined by us in August, 1986. He had directed a wholesale canning business. He was quite successful and his activities extended across the entire Federal Republic of Germany. His past medical history was unremarkable.

The present illness had an insidious onset approximately five years before. In 1981 he had noted problems in recalling the names of people he had met on social occasions, even though he recognized their faces without the slightest difficulty. Yet he was able not only to run his business but to expand it and also to deal with packing material. The disorder evolved to the extent that in 1984 he could not recall the names of regular customers and even of friends. Towards the end of 1985 he developed serious problems in naming objects, even very familiar ones. At the same time he became aware of comprehension difficulties that concerned mainly the meaning of single words and only to some extent the understanding of sentences. Furthermore, he became impaired in reading comprehension so that he virtually stopped reading newspapers and business letters. Spatial orientation was perfect, and he drove without any problems even on unfamiliar routes.

Neurological examination was normal. He was not hypertensive (BP 115/85). The EEG was likewise normal. A CT scan (fig. 4c) showed enlargement of the left sylvian fissure (May 1986) and an MRI examination confirmed this finding. The CSF was normal

M.W. was examined with the AAT in August 1986. The quality of spontaneous speech fluctuated. When conversing at leisure about familiar topics, spontaneous speech was unremarkable. As soon as a topic was discussed in more detail, many empty phrases and stereotypes appeared. There were no phonemic paraphasias. Syntax was complex with some duplication and blending of elements. His level of communication was only slightly impaired.

The following is an example of his spontaneous speech (for original transcript, *see* Appendix 3, 6).

Q: Could you tell me something about your job?

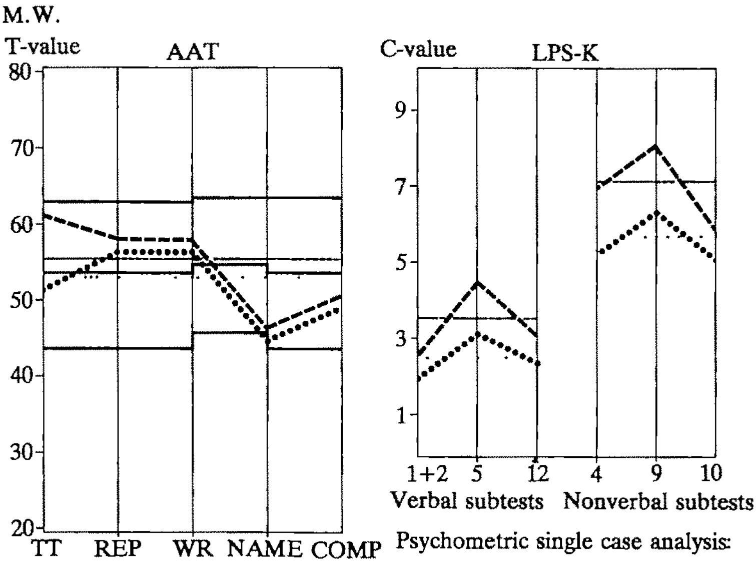
A: At first there was ... well, I was a businessman and my father has .. a ... has ... a ... tin cans . . business founded well in H., where we ... where he also had this business ... and then they have ... they wanted to change something a little bit . only in the field of commerce ... you know ... not in the industrial area ... and then my father opened a wholesale business and ... but only something like three years or something rather and he wished that I also entered the business. When I entered the business ... and then we have tried to change something ... to obtain new customers ... and so ... and then we have provided butchers with tin cans ... and later on we . started to supply other business men ...

In the subtests of the AAT, performance was as follows: Token Test PR 83, Repetition PR 79, Written Language PR 77, Naming PR 34, Comprehension PR 55. Examples of naming errors were as follows.

Table: Well, such a thing in my office, where I am working at, I am sitting in front of it.
Scales· There you put something on, which is the same thing over there.
Typewriter: A letter is made here, I have done all that before. Now it is done by computer.

In Auditory and Reading Comprehension, where a pointing response to a multiple choice set is required, the most striking phenomenon was a frequent 'alienation du mot' (estrangement of word meaning), e.g., stimulus: cup, verbal response: 'cup, cup, what is a cup? I know the word but I really don't know what a cup could be'.

M.W. was further examined for neuropsychological deficit by means of the LPS-K He obtained an IQ of 101 which corresponds to an average performance Analysis of test profiles showed that verbal performances were significantly inferior to nonverbal ones. Performance in reasoning and in spatial subtests was far above average (fig. 3). It was not possible to administer verbal learning and



| SPON | COM | ART | AUT | SEM | PHO | SYN |
|---|---|---|---|---|---|---|
| 1st ex | 3 | 5 | 4 | 3 | 5 | 4 |
| 2nd ex | 3 | 5 | 3 | 3 | 5 | 3 |

Psychometric single case analysis·

| | Comparison<br>1st | 2nd | z | *P* |
|---|---|---|---|---|
| Level of profile | 55.5 | 53.1 | 2.72 | <0.0033 |

Psychometric single case analysis:

| | Comparison<br>1st | 2nd | z | *P* |
|---|---|---|---|---|
| Level of entire profile | 4.75 | 3.67 | 4.24 | <0.0001 |

| Level of the subprofiles | Comparison<br>1st | 2nd | z | *P* |
|---|---|---|---|---|
| Comparison Verbal | 3.57 | 2.55 | 3.19 | <0.0001 |
| Nonverbal | 7.07 | 5.70 | 15.23 | <0.0001 |
| z | −9.32 | −8.50 | | |
| *P* | <0.0001 | <0.0001 | | |

FIG. 3. AAT and LPS-K profiles for *Case 3* For details, *see* legend to fig. 1 1st Examination· August 11, 1986, 2nd examination: February 19, 1987.

memory tasks because the patient was not able to handle the single words stimulus material. Memory span and attention (tested by means of the Digit Span, WAIS) were within the normal range. In the Recurring Figures Test performance was lower than expected (PR 14.8). It appeared that the patient had problems in distinguishing visually between relevant and irrelevant forms There was a high percentage of false positive reactions. Taken together, these findings showed a severe impairment in language dependent in intelligence performance and a slight impairment in the recognition of meaningless forms, whereas visuospatial performance was above average, as was reasoning. M.W. was also given the Progressive Matrices test, and his performance was excellent (51/60). There was no oral or limb apraxia, calculation was good (101/101), and copying of complicated geometric forms was perfect.

A CT scan (fig. 4c) showed circumscribed atrophy of the anterior portion of the left temporal lobe.

M.W. was re-examined in February 1987. The findings are given in fig. 3. Spontaneous speech had deteriorated. There were more stereotyped elements, more word finding difficulties, and syntactic structure was more severely impaired by many blendings, sentence interruptions and incorrect inflections. In the subtests of the AAT, performance was as follows: Token Test PR 56, Repetition PR 74, Written Language PR 75, Naming PR 31, Comprehension PR 49. The profile level had worsened significantly (*see* fig. 3).

In the LPS-K his performance had significantly decreased as compared with the first examination (*see* fig. 3). This was true both for verbal and nonverbal tasks, more so for nonverbal performance, even though this was still within the normal range. Likewise performance in the progressive matrices was still within the normal range, yet the score was lower by 6 points (45/60). This time, M.W. also had problems in calculation. Although mental calculation was still perfect for the four basic arithmetical operations, he was completely unable to perform written divisions requiring 'carry-over' in the intermediate steps of the computation. Nevertheless, he was able to resolve most of the calculations by replacing the divisions with repeated addition of the divisor until the dividend was obtained Although his overall performance was still almost perfect (99/101), he needed 50% more time than in the previous examination for the computation.

### *Radiological findings*

While the neuropsychological syndrome was quite similar in these 3 patients, there were some discrepancies in the neuroradiological findings. Case 3 had persisting circumscribed cortical atrophy restricted to the convexity of the temporal lobe, in particular to its anterior part. Case 1 had a marked degree of atrophy of the left hemisphere particularly affecting the perisylvian areas. Case 2 had bilateral cortical atrophy, in particular of the perisylvian region, slightly pronounced on the left.

## DISCUSSION

The three cases reported here presented with a neuropsychological syndrome that is quite similar to the condition described by Mesulam (1982) as 'Slowly progressive aphasia without generalized dementia'. A neurological condition where a progressive deterioration of language was not paralleled by generalized dementia had been described already at the beginning of the century. The anatomical basis was a restricted cortical degeneration in the absence of vascular, inflammatory, or neoplastic damage.

Pick's first case (1892) had a severe language disorder in association with severe atrophy of the left temporal pole and of the posterior two-thirds of the second and third temporal convolutions. He subsequently described further cases with circumscribed atrophy of the temporal (1904), and parietal and frontal lobes (1906). For that reason the term 'Pick's disease' came to denote any kind of circumscribed slowly progressive cortical atrophy (Rosenfeld, 1909; Gans, 1922; Onari and Spatz, 1926; Stertz, 1926; Malamud and Boyd, 1940). Other authors (Sérieux, 1893; Franceschi, 1908; Mingazzini, 1914) described patients with predominant or exclusive impairment of language function under different headings such as 'aphasic dementia' or 'pure word deafness evolving towards sensory aphasia'.

In the ensuing years the term Pick's disease was applied to a quite different condition, namely a disease state where a derangement of behaviour predominated. Pick's disease was found to have a distinct neuropathological picture, namely restricted involvement of the frontal and/or temporal lobes, characterized histologically by ballooned cells and argentophilic inclusions. Cases of lobar atrophy with circumscribed neuropsychological deficits but without the above mentioned histological features were consequently discussed in the larger context of Alzheimer's disease (Berlin, 1949; Tariska, 1970; Horenstein, 1971).

In the older literature we have found 19 cases with a severe language disturbance not paralleled by a similar degree of other neuropsychological deficits. Only 6 of

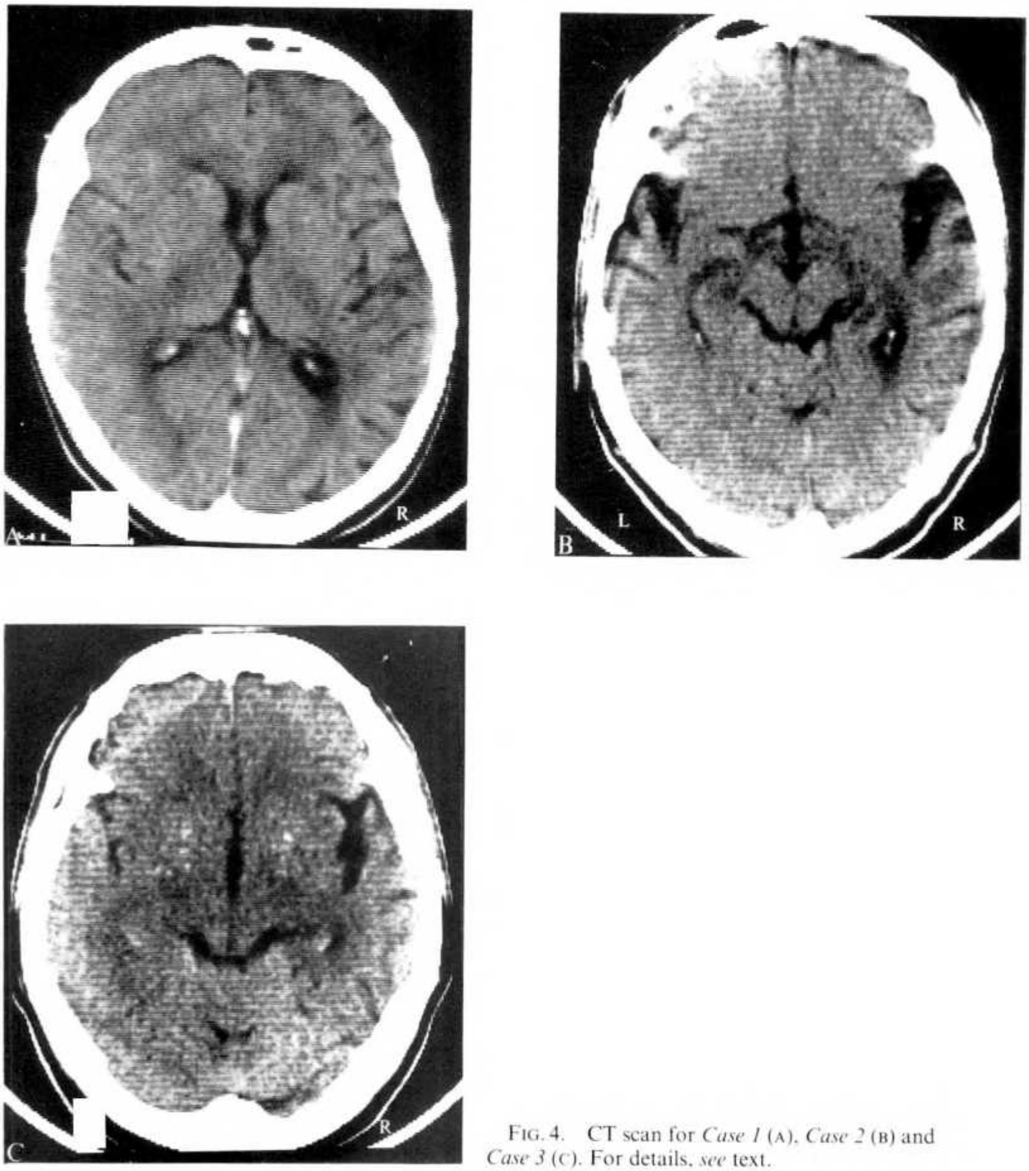


FIG. 4. CT scan for *Case 1* (A), *Case 2* (B) and *Case 3* (C). For details, *see* text.

these patients (Pick, 1982; Sérieux, 1893; Rosenfeld, 1909; Mingazzini, 1914; Stertz, 1926; Malamud and Boyd, 1940) had this dissociation of impairment for a longer period of time (*see* Table). Only 2 of these (Cases D.B. and E.N.) were said to have a relatively pure language deficit until the end of the observation period. The case description and discussion in these 2 cases were, however, not quite in accord with this statement. The patient of Sérieux (1893; Dejerine and Sérieux, 1897), who has already been mentioned by Mesulam (1982), developed severe mental deterioration, while Rosenfeld's patient (1909) obviously had some degree of visual agnosia and probably also a memory deficit. A similar consideration holds true for the patient with 'slowly progressive visual agnosia' described by Taylor and Warrington (1971). The visual agnosia in this patient was accompanied by a conspicuous lexical disorder quite similar to that of our Case 3.

TABLE CASES FROM THE EARLIER LITERATURE WITH CLINICAL FEATURES SUGGESTING A DIAGNOSIS OF SLOWLY PROGRESSIVE LANGUAGE DISORDER

| *Author* | *Case* | *Sex* | *Age at onset (yrs)* | *Length of illness (yrs)* | *Type of aphasia* | *Other neuro-psychological disorders* | *Follow-up (yrs)* | *Type of aphasia* | *Other neuro-psychological disorders* | *Pathology* |
|---|---|---|---|---|---|---|---|---|---|---|
| Pick (1892) | A H | M | 69 | 2 | TS | ± | — | — | — | t (L > R) |
| Sérieux (1893) (Dejerine and Sérieux, 1897) | D B. | F | 47 | 5 | PWD (?) | — | 3 | W | ± | t (bilat ) |
| Rosenfeld (1909) | E N | M | 54 | 8 | A | — | 4 | A | ± | t (L) |
| Mingazzini (1914) | P M | M | 57 | 2 | TS | — | 2 | M | + | t,f (L > R) |
| Stertz (1926) | A B | F | 57 | 8 | W/TS | ± | 3 | TS/M | + | t > p (bilat ) |
| Malamud and Boyd (1940) | A C | F | 54 | 5 | A/W | — | 5 | ? | + | t (bilat ) |

A = amnesic aphasia, PWD = pure word deafness, TS = transcortical sensory aphasia, W = Wernicke's aphasia, M = muteness, t = temporal, p = parietal, f = frontal.

Reviewing the recent literature, we were able to find 29 patients corresponding to Mesulam's description; 24 were described under the heading of a slowly progressive degenerative disorder (Mesulam, 1982; Heath *et al.*, 1983; Gordon and Selnes, 1984; Kirshner *et al.*, 1984; Pogacar and Williams, 1984; Assal *et al.*, 1985; Holland *et al.*, 1985; Chawluk *et al.*, 1986). The 3 cases of Benson *et al.* (1982) have been referred to already in the Introduction. We have added 2 further cases, 1 described by Wechsler (1977) and Wechsler *et al.* (1982), certainly fulfilling the criteria of the syndrome, and the case of Schwartz *et al.* (1979), even though the authors discuss their patient in another context. We have refrained from including the 5 cases with familial aphasia described by Cole *et al.* (1979) and the cases of Morris *et al.* (1984), because the clinical description did not lend itself easily to comparison with the other cases.

If we analyse the language deficit in these cases, a unitary syndrome does not emerge. Instead, a large spectrum of disorders is found, ranging from Broca's aphasia with phonetic disintegration and agrammatism to word deafness or to fluent semantic jargon. Yet the majority of cases exhibit amnesic aphasia which is the language deficit described as the prominent symptom in primary degenerative cortical disease. The amnesic aphasia is, in the great majority of cases, more 'pure' than is commonly encountered in vascular patients. Over the time of follow-up the language disorder evolves to a severe semantic breakdown (Schwartz *et al.*, 1979) while phonology and syntax remain relatively spared. Some patients present with apraxia or acalculia, much the way these symptoms are seen in other cases of aphasia (Lebrun and Hoops, 1974; Basso *et al.*, 1981; Poeck, 1988).

Considering the patients with a follow-up neuropsychological examination, it appears that 7 evolved to a more extensive disorder (Alzheimer's or Pick's syndrome) (Wechsler, 1977; Schwartz *et al.*, 1979; Mesulam, 1982, Cases 3, 6; Pogacar and Williams, 1984; Assal *et al.*, 1985; Holland *et al.*, 1985) while in 7 their language disturbance remained the conspicuous aspect (Mesulam, 1982, Cases 1, 2, 5; Kirshner *et al.*, 1984, Cases 2, 4; Chawluk *et al.*, 1986). The reason for this remarkably high proportion might be that an important requirement, stipulated by Foster and Chase (1983) and Gordon and Selnes (1984), namely the necessity of documenting the presence or absence of a neuropsychological deficit by the performance in standardized tests, was very rarely fulfilled. Standardized tests were in fact applied in less than one-third of the cases.

In our 3 cases the language disturbance remained the only obviously impaired psychological function for a period of five years. This clinical impression was confirmed by a battery of standardized tests, where the patients were found to be severely impaired in tests of verbal intelligence and memory. Performance in tests of nonverbal intelligence and memory, however, calls for a more complex interpretation. It is true that performance in the follow-up examination was still within the normal range. However, a comparison with the results of the first examination by means of psychometric single case analysis clearly showed a statistically significant decline of performance. This finding is also indicative of a slow but progressive deterioration of nonverbal intelligence functions. This deterioration is out of proportion to their degree of decline in language performance and in verbal intelligence tests. It therefore cannot easily be attributed to the well-known impairment in cognitive performances of aphasic patients (Lebrun and Hoops, 1974; Basso *et al.*, 1981). It is tempting to speculate that follow-up examination and statistical comparison of test scores might reveal a similar trend in the majority, if not all, of the cases described as presenting with progressive language disturbance *without* generalized dementia.

## *Conclusions*

The main hypotheses discussed in the recent literature with respect to these and similar cases are (1) that they are examples of an autonomous disease different from the common degenerative diseases (e.g. Mesulam, 1982); (2) that they represent variants of Pick's disease (Wechsler, 1977; Wechsler *et al.*, 1982), where a language disorder constitutes the leading symptom; (3) that they might have a vascular aetiology, as suggested by PET studies (Benson *et al.*, 1982); or (4) that they represent dissociated variants of Alzheimer's disease into which they might eventually evolve (Gordon and Selnes, 1984).

The notion of an autonomous disease is, in our view, not strongly supported by the case reports. Even the 2 allegedly most pure cases in the earlier literature (Dejerine and Sérieux, 1897; Rosenfeld, 1909) eventually evolved to a more complex neuropsychological syndrome. The same might be true for the large majority of patients described in the more recent literature.

The suggestion of a pure temporal lobe variant of Pick's disease is hard to substantiate in the absence of histological data. Our patients did not present, in addition to the language disturbance, with the well-known behavioural syndrome. In the literature pathological data are available for only few similar cases, and are contradictory (Pick vs Alzheimer). The assumption of a vascular basis is, in our view, also not well-founded. These patients do not correspond to the clinical features of multiinfarct dementia (Hachinski *et al.*, 1975). The focal or generalized hypometabolism demonstrated by PET scanning is for that reason more likely to be the result than the cause of a degenerative cerebral process. Our findings appear to justify the hypothesis that these patients have a variant of Alzheimer's disease with a long initial phase of language breakdown followed by the appearance of other neuropsychological deficits.

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## APPENDIX 1 (slightly modified from Willmes, 1985)

*Short description of the AAT and its psychometric properties*

The AAT consists of six 6-point spontaneous speech rating scales and five subtests. *Token Test* (TT), German version of Orgass (1976), *Repetition* (REP), *Written Language* (WRIT), *Confrontation Naming* (NAME), and *Comprehension* (COMP), in which different units (phonemes, monosyllabic and polysyllabic nouns, sentences) and linguistic rules are incorporated. Each subtest is composed of three to five parts having 10 items each. Except for the Token Test, which has dichotomous scoring, the response to all items are scored on a 0–3 scale. Although defined more precisely in linguistic terms, for each subtest the scoring is as follows 3 indicates a correct response, 2, mild or little departure from the stimulus; 1, severe departure from the stimulus, 0, complete error or no response Thus scores range from 50–0 errors for the Token Test, 0–150 for Repetition, 0–90 for Written Language, and 0–150 for Confrontation Naming and Comprehension. In the following, only the five subtests will be of interest.

Validity and reliability studies for the test are based on a sample of 120 aphasic patients (30 of each of the four standard aphasic syndromes) The standardization sample is comprised of 376 aphasic patients (90 globals, 74 Wernicke's, 79 Broca's, 71 amnesic, 62 nonclassifiable aphasics), almost exclusively with vascular aetiology, and 100 control patients (41 left brain-damaged patients without language disorders, 20 right brain-damaged patients, and 30 normal controls).

A nonparametric discriminant analysis program (ALLOC, Habbema *et al.*, 1974) is used routinely for the classification of patients with language disorders It investigates (1) what the (posterior) probability for a new patient is to be aphasic or not and, (2) if the probability for aphasia is at least 80%, what the probability is of belonging to one of the four standard syndromes (global, Wernicke's, Broca's and amnesic aphasia) Only if the highest of the four 'syndrome' probabilities is above 70% is the patient considered to belong to one of the standard aphasic syndrome groups, otherwise, the patient is taken to be nonclassifiable.

Test-retest reliability was studied in 40 patients (10 of each standard syndrome) over an interval of 2 days. High reliability coefficients and no significant changes in level of performance (no practice or learning effects) were found both for patients with duration of aphasia below and above 3 months Thus one can feel confident in attributing substantial (significant) changes in performance to other factors such as spontaneous recovery or language therapy treatment

Several norm tables have been set up for the AAT Based on the whole sample of 376 aphasic patients, raw scores for each subtest are first transformed into centile ranks These centile ranks are then further transformed into T scores. By this 2-step procedure, the nonnormal distributions of raw scores, a problem for all aphasia tests, are turned into (quasi) normally distributed standard scores

## APPENDIX 2

*Description of the shortened version of the Leistungsprufsystem (LPS-K) and its psychometric properties*

The LPS-K is a short form of the LPS, which is an intelligence test battery frequently used in Germany and for which two equivalent forms exist Both consist of six subtests based on Thurstone's intelligence factors· verbal comprehension, reasoning, word fluency, space 2, closure 1, closure 2 Each subtest consists of 40–42 items. Subtests are given under time pressure, i e , the subject usually is not able to complete a subtest within the given time limit

*Verbal tasks*

*Subtests 1 + 2* (factor verbal comprehension) The subject's vocabulary is examined the subject is requested to cross out typing errors in a row of 40 nouns with decreasing familiarity.

*Subtest 5* (factor verbal fluency) The subject is asked to find the correct initial letter within a scrambled word

*Subtest 12* (factor closure) This subtest requires the subject to cross out typing errors in nouns printed with mutilated letters.

*Nonverbal tasks*

*Subtest 4* (factor reasoning) This subtest consists of 40 lines of either letters or figures, each line following a specific rule. The subject is required to find the element in each line which does not follow that rule.

*Subtest 9* (factor space 2). The subject must find the number of planes in a three-dimensional drawing of a geometric figure. Obviously not all planes are visible, yet they have to be counted on the basis of a mental image.

*Subtest 10* (factor closure 2) This task is derived from Gottschaldt's Embedded Figures Test In each item, the subject has to recognize one of six given patterns hidden in the item

The scoring system reflects the number of correct responses for each subtest within the given time limit. Validity and reliability have been tested in a sample of 200 subjects Subtest reliability varies between 0 88 and 0 98 Normative data for several age groups are based on representative samples of 5300 normal subjects. Raw subtest scores are transformed into standardized centile values (C value X = 5, SD = 2)

## APPENDIX 3

*Original transcripts of spontaneous speech samples and responses in the naming subtest*

*1 (p. 5)* Es ist schon etwas länger her da kamen die Kunden und dann .. sagte fragte ich . die Mädchen .. (leise) 'Wie heisst der ?' dann konnt . hab ich es wieder ich habe den Namen vergessen, die sagten dann leise . Dann war's wieder gut

*2 (pp. 7–8)*. Ja, vor drei Tagen, und der Anfang es war sehr einfach da konnte ich das genau so sprechen. Und ich hab nicht gemerkt dass ich weiter mo machen kann, aber der Herr Doktor XY hatte gemerkt dass ich das Sprechen nicht gut machen und ich habe auch so etwas bekommen und dann wurde dann gezeigt dass man das nimmt und dieses und des .. und auf ein Mal . . g . weisse ich was das ist .. dann sage ich . aber ich kann's nicht sagen und das das war das erste was anfing und wo ich merkte bei mir, dass es nicht richtig war.

*3 (pp 11–12)*. Ja, wie fing das an? Es war so, ahm sagen wir mal, das weiss ich jett auch nicht haargenau, verstehn Sie Es kann sein, so zwei drei Jahre . . äh, warten Sie mal, als ich 30 Jahre Dienst hatte, durfte ich zum Kur gehen, neun, öh jetzt is es so, bis dahin rauchte ich ehm dreissig Zigaretten pro Tag, ja. Dann ging ich zur Kur, was der Polizeiarzt dann sagte, es war sinnvoll, dass ich nicht mehr rauchte, ne, und da bin ich mit 'nem Bekannten, mit 'nem Verwandten sogar in Kur gegangen, der rauchte nicht, und oh dann hab ich nur in der Kur öh sechs Kilo Gewicht verloren und dann kam ich zurück und rauchte nicht mehr und das ist jetzt öh und zwar ehe ich 50 wurde, no. und seit der Zeit, ich bin jetzt 56, ne, öh seit der Zeit, rauch ich nicht mehr, das schadet ja auch nicht, a ja, ich hab auch so etwa 14000 Mark gespart (. .)

Ja, dreissig Zigaretten pro Tag, wissen Sie und öh dann bin ich dann aus der Kur zuruckgekommen und hab dann öh ... von den 6 Kilo 5 Kilo ehm ein bisschen mehr gegessen, ne, also Ersatz ja, ich bin, einvierundachtzig groß .

*4 (p. 13)* Koffer. Wo ich was reintun kann, was ich mit mir mitnehmen muss. Besen: zum kehren. Kerze Nun, beispielsweise Weihnachten, da brauchen wir die. Bagger: Tja es ist nicht direkt ein Auto, da fahren wir nicht mit. Die Bauern, die brauchen die. Staubsauger: Ja, ist das ein Sauggerät, oder? Kühlschrank. Ein kleines Schränkchen Wo wat drinnen ist. Hubschrauber: Ein Flieger. Schraubenzieher Nun, ich weiss genau, was ich damit zu tun hab.

*5 (pp. 14–15)* Nun das war so, ich war beim Dr XY, öh, da ich bin immer bei ihn, no und hat auch nachher schriftlich mitgeteilt, dass ich nach hier kommen sollte ( ..). Tja, dann hab ich Medikamente eingenommen, hab ich mitgebracht, öhm ich sag alle Medikamente die ich einzunehmen hatte, ja ja gebessert hat sich nichts, verstehn Sie. Wenn Sie jetzt lesen, naja und jetz ist da so, und so viele Worte, man weiss nicht mehr was sie sind, verstehn Sie? Aber wenn ich die Moglichkeit hatt, angenommen ich lese jetz, öhm ein Stück, no wenn da 10 Worte sind die man nicht mehr weiss, was ist das, tja, jetzt würde ich das genau prufen und ich wurde das, und wahrscheinlich hätt ich das dann, naja, dann wurde man doch lieber lesen.

*6 (pp 18–19)*. Zuerst war da, tja, ich bin Geschaftsmann und mein Vater hat ... eine . . hat . ein Konserven dosen . geschaft gegründet . get in H. wo wir ... wo er auch disen Betrieb hatte . und dann haben sie ... sie wollten etwas ein bisschen ändern nur in dem Handelsbereich .. wissen Sie . nicht im Industriegebiet .. und dann hat mein Vater einen Konservendosengrosshandel gemacht und . aber nur so für drei Jahre oder so eigentlich und er wollte, daß ich mit im Geschäft geh Wie ich im Geschaft einstieg ... und dann haben wir versucht ... etwas zu andern, ... neue Kunden kriegen . und so . . und dann haben wir nur Metzger beliefert . . und später fingen wir an, andere Handler zu beliefern ..

Tisch: Nun, so was in meinem Büro, wo ich arbeite, ich sitze ja vorne dran. Waage. Da wird etwas hingelegt, was das gleich ist da druben. Schreibmaschine: Ein Brief . . wird hier gemacht, ich habe das alles schon gemacht. Jetzt macht man's mit Computer gemacht.

*Brain* (1988), 111, 169–184

# INTELLECTUAL FUNCTION FOLLOWING PENETRATING HEAD INJURY IN VIETNAM VETERANS

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## SUMMARY

The extent to which intellectual processes are preserved as a function of preinjury 'intelligence' and of size and location of the brain lesions was evaluated in Vietnam war veterans who survived penetrating missile wounds. With regard to an overall postinjury intelligence test score, preinjury intelligence was most predictive, size of lesion was next most predictive and lesion location was least important. For subtest scores from the same intelligence test, lesion location assumed much greater predictive value. Specifically, left temporal and occipital lesions impaired performance on subtests assessing vocabulary and object-function matching ability.

## INTRODUCTION

Neuropsychological studies on changes in 'intelligence' before and after brain injury are relatively rare, largely because preinjury psychometric data are usually absent (Piercy, 1964). In military personnel, preinjury data in the form of a general intelligence-type classification test are usually available. Since combat soldiers are generally healthy, of a uniform age and sex, have reasonably equivalent educational levels, and as a group are symmetrically distributed on a preinjury classification test, they compose an ideal population in which to study the cognitive sequelae of brain injury. This study was designed to address the effects of preinjury intellectual ability and the signficance of lesion location and size in persistence of intellectual dysfunction following brain injury.

Teuber and associates (Teuber *et al.*, 1952; Weinstein *et al.*, 1957*a*; Teuber, 1959), in studying 62 World War II veterans with penetrating brain wounds, found that 'intellectual' deficits in the posterior lesion group equalled or surpassed those

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found in the group with anterior lesions. Comparison of preinjury and postinjury performance on the Army General Classification Test (AGCT), an intelligence test composed of various linguistic and nonverbal subtests, showed that left parietal and/or temporal lobe lesions resulted in a significant decline in IQ scores, even when patient samples only included 'nonaphasic' patients. All other unilateral lesion groups showed either no change in scores or marked improvement. These studies also showed no relationship between preinjury education and pre- to postinjury AGCT score changes. However, Teuber did not report on the relationships between preinjury AGCT score and pre- to postinjury score changes.

Grafman *et al.* (1986) examined the relationship of size and location of lesion to postinjury cognitive deficit in Vietnam veterans who sustained a penetrating missile wound injury to the brain and found that volume loss accounted for a larger part of the variance when performance was evaluated by a global measure (e.g., an IQ score), whereas lesion location (i.e., specific neural structures) accounted for a larger part of the variance when performance was evaluated by a specific measure (e.g., performance on a test of spatial rotation). Interestingly, preinjury intellectual level (as measured by a military induction classification test percentile score) played a much larger role than either volume loss or lesion location in predicting postinjury cognitive performance level.

The question as to how preinjury cognitive status affects postinjury cognitive performance is not a trivial one. Psychometric and neuropsychological issues such as test-retest reliability, regression to the mean, learning potential, motivation, hemisphere differences in processing similar stimuli, lesion size and location, all complicate interpretation of the effects of preinjury cognitive ability. In order to address some of these issues, we have extended our earlier study (Grafman *et al.*, 1986) by focusing on the Armed Forces Qualification Test (AFQT). We were able to study veterans who were wounded during combat in Vietnam and had received the AFQT at induction (preinjury) and again some 15 years later (in the Vietnam Head Injury Study). In the study reported below, we examined pre- to postinjury changes in percentile score (D-AFQT), preinjury education effects on postinjury performance, and the effects of lesion site and size on both AFQT percentile and subtest scores.

## METHODS

The Vietnam Head Injury Study (VHIS), an extensive inpatient multidisciplinary reevaluation of over 600 head-injured veterans and controls at 12–15 yrs postinjury, used CT scanning to determine brain volume loss and lesion location, and standardized templates to code involved anatomical structures for computer entry and subsequent analysis. Lesion location and volume were determined by a computerized tomography (CT) scan procedure/software program specifically devised for our study. CT scans were performed with a GE 8800 scanner in standardized 5 mm cuts at approximately 25° to Reid's baseline, yielding about 24 slices per patient. Involvement of over 80 specific brain areas was coded for computer entry by the use of standard templates prepared for each slice, assigning code numbers to each area. Structures only partly involved on CT were considered to be completely involved for our analysis; thus, we included potential areas of hypofunctioning tissue surrounding the CT defect. As a further aid in localization, a corresponding photographic anatomical atlas was prepared by slicing a fresh-frozen specimen in situ at the same angle on a large cryotome, and photographing it at 1 mm intervals, which yielded over 130 brain sections. Image analysis included both a subjective morphological interpretation and a quantitative lesion analysis using a light pen to outline the affected area in each slice. Total lesion volume was then calculated from a summation of these areas on relevant slices. When our CT scan results were compared with estimates of lesion extent based on the original surgical notes and skull x-rays, we found approximately 100% more multilobe lesions than expected (*see also* Carey *et al.*, 1984) It is likely that studies completed before the availability of CT scanning also grossly underestimated the extent of their patients' lesions (Teuber *et al.*, 1952, Weinstein *et al.*, 1957*a*, *b*; Teuber, 1959, Newcombe, 1969, Black, 1973).

The VHIS registry includes veterans who survived the first week after penetrating (fragment or gunshot) head injury and on whom we have detailed initial and follow-up hospital records; 520 of them volunteered to participate in the VHIS follow-up examination. All subjects are males (average age at injury is 21 ± 3 yrs). Subjects excluded (1) were either left-handed before their injury, (2) had learned English as a second language, (3) were blind in either eye, (4) had Broca's, Wernicke's, conduction, transcortical sensory or transcortical motor aphasias, (5) suffered other central nervous system insult, or (6) did not have pre- and/or post-AFQT score data available. Uninjured control subjects served in Vietnam during the same years as the head-injured subjects and were stratified-matched with brain-injured patients on preinjury AFQT scores. This test, a general measure of intelligence, was readministered to all subjects at the VHIS. This report is based on 263 brain-injured patients and 64 controls who met inclusion criteria There was no significant difference between any of the experimental groups (including controls) on age, education, or preinjury AFQT percentile scores (Table 1). Postinjury AFQT percentile scores (*see* below) for our entire sample were also symmetrically distributed.

TABLE 1 CHARACTERISTICS OF SUBJECTS BY LESION GROUP MEANS(SD)

| | *Controls* | *Right hemisphere* | *Left hemisphere* | *Bilateral* |
|---|---|---|---|---|
| Number | 64 | 96 | 78 | 89 |
| Age (yrs) | 36.23<br>(1.75) | 35.61<br>(2.12) | 35.97<br>(2.81) | 36.03<br>(3.43) |
| Postinjury education (yrs) | 14.00<br>(2.26) | 13.29<br>(2.40) | 13.61<br>(2.57) | 13.56<br>(2.02) |
| Pre-injury AFQT (score) | 59.17<br>(25.23) | 55.00<br>(23.83) | 57.79<br>(27.47) | 56.17<br>(24.98) |
| Pre- to postinjury AFQT difference* | 9.43<br>(14.71) | 1.33<br>(17.17) | 3.12<br>(16.76) | −1.73<br>(18.77) |
| Total brain volume loss (cc) | —<br>— | 34.31<br>(44.70) | 23.37<br>(20.76) | 50.32<br>(37.58) |

ANOVA significance level $^{*}P \leq 0.01$

The AFQT was administered individually with a 50 min time limit. Instructions were presented orally with the patient reading them simultaneously. The test was composed of four subtests: vocabulary knowledge, arithmetic word problems, object-function matching, and 'mental' imagery construction of boxes (fig. 1). Patients chose from a multiple choice solution (four choices), and items left unanswered were scored as incomplete. Each score was converted to a percentile score via standard tables derived from military inductee performance. In order not to penalize subjects for slowness, subtest scores were recorded as the ratio of the number of items correct to the number of items completed.

A

1. The boys discovered the cave
   (A) Searched
   (B) Found
   (C) Enlarged
   (D) Entered

B

5. Bob wants to buy a wagon. He has 5 dollars and needs 5 dollars more. How much does the wagon cost?
   (A) $10
   (B) $15
   (C) $25
   (D) $55

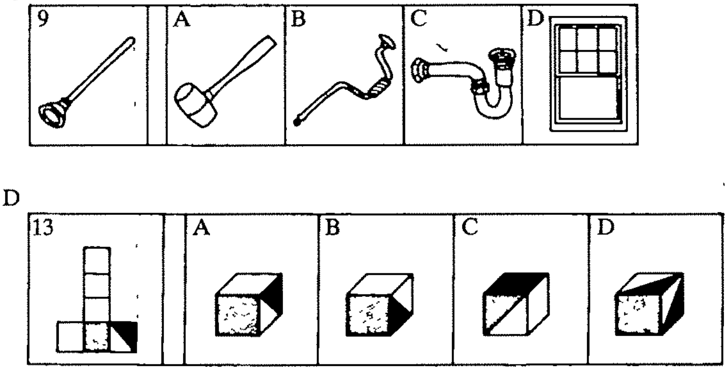

FIG. 1 Sample items from the vocabulary (A), arithmetic (B), objects (C), and boxes (D) subtests of the Armed Forces Qualification Test (AFQT). For the objects and boxes subtests, the stimulus item is on the far left and subject must choose either the correct associate (C) or the correct figure (D) from the four choices to the right.

## RESULTS

### *Preinjury AFQT percentile scores and pre- to postinjury differences*

Table 2 presents a correlation matrix for the principal measures analysed. The correlation between preinjury and postinjury AFQT ($r = 0.76$, $P < 0.0001$) is highly significant. The correlation between pre- to postinjury AFQT difference score (D-AFQT) and postinjury AFQT ($r = 0.37$, $P < 0.0001$) is also significant, although not nearly as high as the pre- and postinjury measures. The correlation between preinjury AFQT and D-AFQT ($r = -0.32$, $P < 0.0001$) is significantly negative. This implies that as preinjury AFQT scores increase, the ‘gains’ (difference scores) will be less. Figs 2 and 3 highlight the first and third of these relationships for patients and controls. The figures show that preinjury AFQT scores have opposite relationships when correlated with postinjury AFQT scores (significantly positive) and D-AFQT (significantly negative). For the controls, similar patterns were observed (Table 3). The correlation between preinjury and postinjury AFQT ($r = 0.81$, $P < 0.0001$) is highly significant, while the correlation between preinjury AFQT and D-AFQT ($r = -0.44$, $P < 0.0001$) is significantly negative. The chief difference in the plotted relationships for controls (figs 2, 3) is displacement of the curves. The curve for pre-AFQT with D-AFQT, for example, is shifted 5–10 points higher for the controls, representing their significantly higher gains as compared with the brain-injured groups. In both figures, the eighth decile for the control group represents only 2 patients. Thus the dips in the curve may be considered statistical artefact.

An analysis of variance of D-AFQT with patients grouped by preinjury quintile indicated that those patients who had lower preinjury AFQTs were most likely to

TABLE 2 CORRELATION MATRIX CASES ONLY (n=263)

| | *Post-AFQT* | *Pre-AFQT* | *D-AFQT* | *Educ pre* | *Tot loss* | *Boston naming* | *Token Test* | *Token Reading* | *Loss cons* | *Epilepsy* | *Hemianopia* | *Paresis* | *Alcohol* | *Marijuana* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Post-AFQT | 1.00 | 0.76 | 0.37 | 0.40 | −0.22 | 0.59 | 0.32 | 0.50 | −0.11 | −0.20 | −0.19 | −0.17 | 0.05 | 0.00 |
| Pre-AFQT | | 1.00 | −0.32 | 0.44 | 0.05 | 0.59 | 0.22 | 0.37 | 0.04 | −0.17 | −0.08 | −0.01 | 0.00 | −0.09 |
| D-AFQT | | | 1.00 | −0.04 | −0.42 | 0.01 | 0.14 | 0.18 | −0.23 | −0.06 | −0.16 | −0.23 | 0.00 | 0.13 |
| Education pre | | | | 1.00 | 0.02 | 0.32 | 0.17 | 0.22 | 0.10 | −0.04 | −0.07 | 0.06 | 0.01 | 0.00 |
| Total volume loss | | | | | 1.00 | 0.01 | −0.08 | −0.08 | 0.31 | 0.24 | 0.32 | 0.48 | −0.04 | −0.10 |
| Boston Naming Test | | | | | | 1.00 | 0.27 | 0.36 | −0.09 | −0.07 | −0.12 | 0.01 | 0.10 | 0.05 |
| Token Test | | | | | | | 1.00 | 0.47 | −0.15 | −0.16 | −0.18 | −0.13 | 0.08 | 0.09 |
| Token Reading Test | | | | | | | | 1.00 | −0.09 | −0.16 | −0.24 | −0.16 | −0.01 | 0.04 |
| Loss of consciousness | | | | | | | | | 1.00 | 0.09 | 0.11 | 0.19 | −0.01 | 0.00 |
| Epilepsy | | | | | | | | | | 1.00 | 0.06 | 0.20 | −0.05 | 0.02 |
| Hemianopia | | | | | | | | | | | 1.00 | 0.11 | −0.05 | −0.05 |
| Paresis | | | | | | | | | | | | 1.00 | 0.04 | −0.08 |
| Alcohol | | | | | | | | | | | | | 1.00 | 0.10 |
| Marijuana | | | | | | | | | | | | | | 1.00 |

| r | <0.15 | 0.15–0.20 | 0.20–0.25 | 0.25+ |
|---|---|---|---|---|
| *P* value | n.s. | *P*<0.01 | *P*<0.001 | *P*<0.0001 |

TABLE 3 CORRELATION MATRIX CONTROLS (n=64)

| | *Post-AFQT* | *Pre-AFQT* | *D-AFQT* | *Educ pre* | *Tot loss* | *Boston naming* | *Token Test* | *Token Reading* | *Loss cons* | *Epilepsy* | *Hemianopia* | *Paresis* | *Alcohol* | *Marijuana* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Post-AFQT | 1.00 | 0.81 | 0.15 | 0.23 | — | 0.69 | 0.30 | 0.43 | — | — | — | — | 0.00 | −0.13 |
| Pre-AFQT | | 1.00 | −0.44 | 0.25 | — | 0.54 | 0.41 | 0.50 | — | — | — | — | −0.05 | −0.09 |
| D-AFQT | | | 1.00 | −0.05 | — | 0.14 | −0.24 | −0.19 | — | — | — | — | 0.09 | −0.04 |
| Education pre | | | | 1.00 | — | 0.30 | −0.10 | 0.13 | — | — | — | — | −0.05 | −0.01 |
| Total volume loss | | | | | — | — | — | — | — | — | — | — | — | — |
| Boston Naming Test | | | | | | 1.00 | 0.25 | 0.33 | — | — | — | — | −0.08 | 0.00 |
| Token Test | | | | | | | 1.00 | 0.34 | — | — | — | — | −0.15 | 0.00 |
| Token Reading Test | | | | | | | | 1.00 | — | — | — | — | −0.03 | 0.03 |
| Loss of consciousness | | | | | | | | | — | — | — | — | — | — |
| Epilepsy | | | | | | | | | | — | — | — | — | — |
| Hemianopia | | | | | | | | | | | — | — | — | — |
| Paresis | | | | | | | | | | | | — | — | — |
| Alcohol | | | | | | | | | | | | | 1.00 | −0.01 |
| Marijuana | | | | | | | | | | | | | | 1.00 |

| r | <0.33 | 0.33–0.38 | 0.38–0.44 | 0.44+ |
|---|---|---|---|---|
| *P* value | n.s. | *P*<0.01 | *P*<0.001 | *P*<0.0001 |

show gains, while those with higher preinjury AFQT percentile scores tended to stay the same or decline. This pattern held, regardless of whether the lesion was on the right ($F(4,91)=3.37$, $P=0.0127$), left ($F(4,73)=3.57$, $P=0.0103$), or bilateral ($F(4,84)=2.60$, $P=0.0415$) (Table 4).

TABLE 4 PRE- TO POSTINJURY AFQT PERCENTILE SCORE DIFFERENCE BY PREINJURY AFQT QUINTILES AND LESION GROUP MEANS (SD)

| | | *Pre-injury AFQT quintiles* | | | | |
|---|---|---|---|---|---|---|
| *Lesion group* | | *1–20* | *21–40* | *41–60* | *61–80* | *81–99* |
| All head-injured** | n | 28 | 57 | 51 | 69 | 58 |
| | | 9.00 | 5.94 | 2.03 | −0.14 | −8.05 |
| | | (10.74) | (14.36) | (23.11) | (18.08) | (13.24) |
| Right hemisphere* | n | 12 | 17 | 25 | 25 | 17 |
| | | 11.25 | 1.70 | 1.04 | 4.36 | −10.05 |
| | | (11.99) | (11.88) | (21.04) | (16.03) | (15.34) |
| Left hemisphere* | n | 10 | 15 | 10 | 23 | 20 |
| | | 8.20 | 11.13 | 11.80 | −2.08 | −3.75 |
| | | (11.39) | (15.49) | (25.55) | (17.08) | (8.21) |
| Bilateral* | n | 6 | 25 | 16 | 21 | 21 |
| | | 5.83 | 5.72 | −2.50 | −3.38 | −10.52 |
| | | (6.91) | (14.76) | (24.36) | (21.00) | (14.80) |
| Controls** | n | 4 | 17 | 11 | 12 | 20 |
| | | 13.50 | 14.29 | 19.63 | 3.58 | 2.40 |
| | | (20.74) | (12.76) | (14.06) | (18.99) | (6.40) |

ANOVA significance levels $^*P<0.05$, $^{**}P<0.001$.

When all brain-injured patients were combined, the effect of preinjury performance on D-AFQT was highly significant ($F(4,258)=7.08$, $P<0.0001$). Similarly, control group D-AFQTs are negatively correlated with pretest AFQT score ($r=-0.44$, $P=0.0002$). The highest score gains are made in the midrange percentile scores preinjury with higher range scores falling victim to a ceiling effect and lower range scores similarly a victim of regression towards the mean due to floor effects ($F(4,59)=4.18$, $P=0.0048$).

### *Statistical considerations*

The inverse relationship between preinjury AFQT and D-AFQT is actually to be expected, as can be demonstrated by using the covariance operator.

Let X = pretest such that the variance of X = 1, (VAR [X] = 1).

Let Y = posttest such that the variance of Y = 1, (VAR [Y] = 1).

Then the covariance of X and Y (COV [X,Y]) = the correlation of X and Y (CORR [X,Y]).

Let CORR (X,Y) = Rxy and assume Rxy > O, i.e., Rxy is positive.

Let Y-X = pre- to postdifference score ('raw gain').

$$\begin{aligned}\text{Then COV }(X,Y\text{-}X) &= \text{COV }(X,Y) - \text{COV }(X^2)\\ &= \text{COV }(X,Y) - \text{VAR }(X)\\ &= Rxy - 1\end{aligned}$$

Therefore, when Rxy is positive, the difference score, Y-X, is negatively correlated with pretest score

There are three points to be emphasized here. The first is that the reverse relationships discussed are expected due to the fact that the difference score (Y-X) is a mathematical function of Y and X, thus interdependent on their relationships The second is that the percentile scores are limited by ending points namely 0 and 100%. Thus extreme scores will be influenced by floor and ceiling effects. This also explains why it is intuitively reasonable that the preinjury AFQT to D-AFQT correlation should be negative, since prescores near the bottom of the percentile distribution can almost only rise, while those near the top can almost only fall. However, figs 2 and 3 demonstrate that this inverse

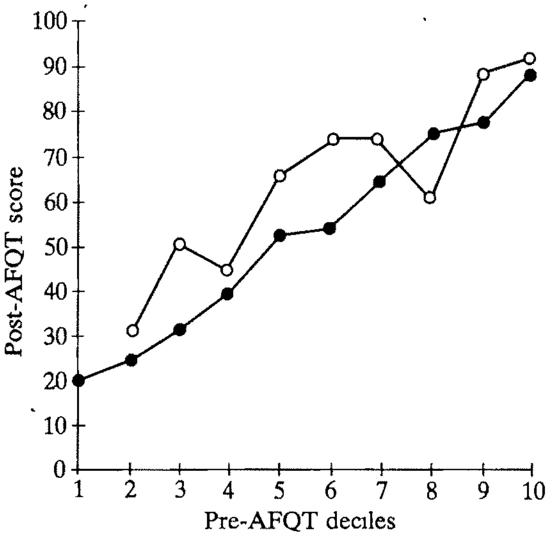

FIG 2 Pre- and postinjury Armed Forces Qualification Test scores (AFQT) in Vietnam Head Injury Study (VHIS) patients (filled circles, r = 0.86) and controls (open circles, r = 0.81) Plot of postinjury AFQT scores by preinjury AFQT deciles

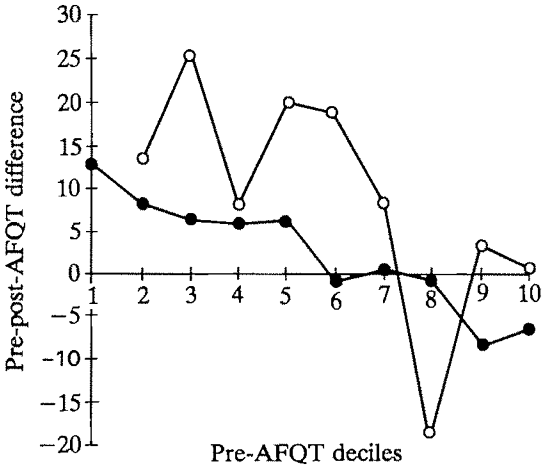

FIG 3. Pre- and postinjury Armed Forces Qualification Test scores (AFQT) in Vietnam Head Injury Study (VHIS) patients (filled circles, r = −0.32) and controls (open circles, r = −0 44). Plot of pre- to postinjury AFQT Differences (D-AFQT) by preinjury AFQT deciles

relationship generally holds throughout the entire range of pre-AFQT test scores. Lastly, since the difference score is correlated with pretest score, it is necessary to account for the effect of pretest score before considering the effects of any other variables on the difference score (D-AFQT). It can be shown that 'residualized gain', namely, the remaining error of prediction after pretest scores, are regressed on posttest scores, is uncorrelated with pretest status Thus by adjusting for pretest variance first, we can assess the importance of other measures independent of the pretest score

### *Preinjury education level*

When categorized by *achieved preinjury education level*, there were virtually no pre- to postinjury AFQT percentile score differences between groups (some high school, high school graduate, some college, college graduate and above) for all head injured patients (Table 5). Similarly, when broken down by lesion group, neither right nor left hemisphere cases, bilateral cases nor controls showed significant findings. However, since pre-AFQT percentile score is significantly negatively correlated with D-AFQT, it is noteworthy that preinjury education level is uncorrelated with the percentile score difference. Further analysis of the data

TABLE 5 PRE- AND POSTINJURY AFQT PERCENTILE AND SCORE DIFFERENCES BY PREINJURY EDUCATION[1] AND LESION GROUP MEANS

| | | *Pre-injury education level* | | | |
|---|---|---|---|---|---|
| *Lesion group* | | *Some high school* | *High school grade* | *Some college* | *College grade and above* |
| All head-injured | n | 57 | 114 | 67 | 24 |
| Pre-AFQT | | 41.19 | 53.50 | 67.03 | 74.33 |
| Post-AFQT | | 42.63 | 54.95 | 66.49 | 74.00 |
| D-AFQT | | +1.44 | +1.45 | −0.54 | −0.33 |
| Right hemisphere | n | 26 | 39 | 22 | 9 |
| Pre-AFQT | | 45.57 | 53.18 | 62.41 | 72.00 |
| Post-AFQT | | 45.38 | 56.20 | 63.09 | 72.00 |
| D-AFQT | | −0.19 | +3.02 | +0.68 | 0.00 |
| Left hemisphere | n | 15 | 33 | 19 | 10 |
| Pre-AFQT | | 41.27 | 50.75 | 70.63 | 80.70 |
| Post-AFQT | | 42.20 | 57.51 | 72.47 | 76.40 |
| D-AFQT | | +0.93 | +6.76 | +1.84 | −4.30 |
| Bilateral | n | 16 | 42 | 26 | 5 |
| Pre-AFQT | | 34.00 | 55.97 | 68.31 | 65.80 |
| Post-AFQT | | 38.56 | 51.78 | 65.00 | 72.80 |
| D-AFQT | | +4.56 | −4.19 | −3.31 | 7.00 |
| Controls | n | 3 | 24 | 21 | 15 |
| Pre-AFQT | | 48.00 | 51.25 | 65.09 | 65.40 |
| Post-AFQT | | 70.33 | 60.04 | 72.19 | 76.20 |
| D-AFQT | | +22.33 | +8.79 | +7.09 | +10.80 |

[1] Total sample sizes do not add up because of 1 missing head-injured and 1 missing control value on the pre-injury education variable ANOVAs showed no significant differences

indicated that for brain-injured cases in the lower half of the preinjury AFQT percentile score distribution, there was a marginally significant relationship between preinjury education level and the percentile score difference. For this lower AFQT group, only cases with higher preinjury education (some college) made significantly greater gains (t = 2.01, $P = 0.0432$) than those cases with lower education (some high school) after adjusting for the effects of preinjury AFQT. Analysis of the upper half of the preinjury score distribution revealed no significant effects, hence the overall effect of achieved preinjury education level was not significant.

### *Total brain volume loss*

As expected for all head-injured patients, the effect of increasing total brain volume loss was highly significant (F(3,238) = 16.50, $P < 0.0001$) (*see* Table 6). As brain volume loss increases to over 50 cc, the average D-AFQT is negative, while losses less than 50 cc are positive. Using groupings of 0–25 cc, 25–50 cc, 50–75 cc and 75+ cc, Tukey comparisons reveal that all groups are significantly different from each other in mean percentile score difference values.

When analysed separately by lesion group, each group showed similar significant results. For the right hemisphere (F(3,84) = 6.15, $P = 0.0009$), the differences are between <75 cc and 75+ cc groups. For the left hemisphere (F(3,68) = 4.37, $P = 0.0073$), the differences are between <25 cc and 50+ cc groups. For bilateral

TABLE 6 PRE- AND POSTINJURY AFQT PERCENTILE AND SCORE DIFFERENCES BY TOTAL BRAIN VOLUME LOSS[1] (IN CC) AND LESION GROUP MEANS.

| | | *Total brain volume loss* | | | |
|---|---|---|---|---|---|
| *Lesion group* | | *0–25* | *25–50* | *50–75* | *75+* |
| All head-injured | n | 120 | 62 | 27 | 33 |
| Pre-AFQT | | 54.78 | 58.32 | 62.03 | 57.12 |
| Post-AFQT | | 60.65 | 58.83 | 55.18 | 43.09 |
| D-AFQT** | | +5.87 | +0.51 | +0.51 | −14.03 |
| Right hemisphere | n | 50 | 18 | 9 | 11 |
| Pre-AFQT | | 57.58 | 55.05 | 49.88 | 57.74 |
| Post-AFQT | | 61.60 | 56.77 | 49.22 | 40.36 |
| D-AFQT** | | +4.02 | +1.72 | −0.66 | −17.18 |
| Left hemisphere | n | 45 | 20 | 4 | 3 |
| Pre-AFQT | | 53.07 | 67.95 | 73.25 | 45.66 |
| Post-AFQT | | 60.91 | 67.55 | 60.50 | 33.00 |
| D-AFQT* | | +7.84 | −0.40 | −12.75 | −12.66 |
| Bilateral | n | 25 | 24 | 14 | 19 |
| Pre-AFQT | | 52.28 | 52.75 | 66.64 | 58.68 |
| Post-AFQT | | 58.32 | 53.12 | 57.50 | 46.26 |
| D-AFQT* | | +6.04 | +0.37 | −9.14 | −12.42 |

[1] Total sample sizes do not add up because of 20 missing values on the total brain volume loss variable. ANOVA significance levels: * $P \leqslant 0.01$, ** $P \leqslant 0.001$

cases (F(3,78) = 4.45, $P = 0.0063$), the differences similarly are between <25 cc and 50+ cc groupings.

*Lesion location*

When categorized by *lesion side* (left, right, and bilateral), there was a statistically significant difference between the mean control group D-AFQT (which indicated a substantial improvement from initial to current AFQT performance) and the brain-injured patients' scores (which tended to remain somewhat stable or show a slight decrease (F(3,323) = 5.52, $P = 0.0012$) (Table 1). There was no difference between the three brain-injured groups on D-AFQTs.

In order to determine the effects of regional lesion location upon post-AFQT performance, we used an analysis of covariance (covarying pre-AFQT scores and total brain tissue loss) on all unilateral lesion cases, with major effects of lobe involvement contrasted by t tests. We also examined lobe effects separately within right hemisphere lesion and left hemisphere lesion groups, considering frontal; temporal, and parietal or occipital (only) lobe effects plus frontal-temporal and parietal-occipital interactions as independent variables (lobe effects) in our model. Overall, 109 brain-injured cases were analysed (the 29 bilateral cases were excluded from this analysis of lobe effects).

For all unilateral cases, as well as right or left hemisphere lesion groups, there were no significant lobe effects on D-AFQT (*see* Table 7). However, as expected (*see* above, Table 6), the D-AFQTs were significantly affected by covarying total brain volume loss for all unilateral cases ($t = 2.12$, $P = 0.0350$), and the left hemisphere lesion groups ($t = 2.41$, $P = 0.0197$). This did not reach significance for patients with right hemisphere injury.

The effects of regional lesion location upon post-AFQT subtest score ratios were studied with an analysis of covariance (covarying total brain tissue loss) on all unilateral lesion cases with major effects of lobe involvement contrasted by t tests (*see* Table 8). No preinjury subtest score ratios were available and pre-AFQT score was not considered appropriate as a covariate in this case, since the overall percentile measure does not directly relate to the proportion of correct items attempted on any one subtest.

For all unilateral cases, as well as right or left hemisphere lesion groups, there was no significant effect associated with covarying total brain volume loss. Furthermore, for unilateral cases the arithmetic and boxes subtests were not differentially affected by lobe involved. Poorer vocabulary performance, however, was elicited from patients with temporal ($t = 2.17$, $P = 0.0322$) or occipital ($t = 2.97$, $P = 0.0038$) involvement. Poorer object-function matching performance was elicited from patients with temporal ($t = 2.04$, $P = 0.0438$) involvement. Within right hemisphere lesion groups, there were no significant effects of lesion location on the subtest completion scores. Within left hemisphere lesion groups, arithmetic and boxes subtests were not differentially affected by lobe involvement. However,

TABLE 7 PRE- AND POSTINJURY AFQT PERCENTILES AND SCORE DIFFERENCES BY SELECTED LOBE EFFECTS[1] AND GROUP MEANS

| | | *Selected lobe effects* | | | | | |
|---|---|---|---|---|---|---|---|
| *Lesion group* | | *Frontal only* | *Temporal only* | *Parietal only* | *Occipital only* | *Frontal temporal* | *Parietal occipital* |
| All head-injured | n | 47 | 24 | 31 | 10 | 10 | 16 |
| Pre-AFQT | | 53.23 | 50.70 | 57.54 | 43.20 | 66.10 | 63.50 |
| Post-AFQT | | 57.40 | 49.58 | 59.87 | 55.50 | 67.40 | 61.87 |
| D-AFQT | | +4.17 | −1.23 | +2.32 | +12.30 | +1.30 | −1.62 |
| All unilaterals | n | 37 | 13 | 28 | 9 | 10 | 15 |
| Pre-AFQT | | 55.24 | 54.38 | 58.71 | 38.56 | 66.10 | 61.86 |
| Post-AFQT | | 61.13 | 51.69 | 62.43 | 51.78 | 67.40 | 62.93 |
| D-AFQT | | 5.88 | −2.69 | +3.71 | +13.22 | +1.29 | 1.06 |
| Right hemisphere | n | 19 | 5 | 17 | 5 | 3 | 7 |
| Pre-AFQT | | 51.52 | 55.40 | 56.94 | 51.60 | 61.33 | 56.43 |
| Post-AFQT | | 56.47 | 53.60 | 59.88 | 64.20 | 64.66 | 58.14 |
| D-AFQT | | 4.95 | −1.80 | +2.94 | +12.60 | +3.33 | +1.71 |
| Left hemisphere | n | 18 | 8 | 11 | 4 | 7 | 8 |
| Pre-AFQT | | 59.17 | 53.75 | 61.45 | 22.25 | 68.14 | 66.62 |
| Post-AFQT | | 66.05 | 50.50 | 66.36 | 36.25 | 68.57 | 67.12 |
| D-AFQT | | +6.88 | −3.25 | +4.91 | +14.00 | +0.42 | +0.50 |
| Bilateral | n | 10 | 11 | 3 | 1 | — | 1 |
| Pre-AFQT | | 45.80 | 46.36 | 46.66 | 85.00 | — | 88.00 |
| Post-AFQT | | 48.60 | 47.09 | 36.00 | 89.00 | — | 46.00 |
| D-AFQT | | −2.20 | +0.72 | −10.66 | +4.00 | — | −42.00 |

[1] Total sample sizes are reduced because of the inclusion of 138 cases that had the specified selected lobe effects ANOVAs showed no significant difference for D-AFQT. The 'Bilateral' and 'All head-injured' groups are shown for descriptive purposes only and were not included in the ANOVAs.

performance on vocabulary was impaired by temporal (t = 2.03, $P = 0.0481$) and occipital lobe involvement (t = 2.99, $P = 0.0044$). Performance on the object-function matching subtest was impaired by temporal lobe involvement (t = 2.32, $P = 0.0244$).

These results suggest that loss in total brain volume plays a large role when global scores (e.g., pre- to postinjury AFQT percentile difference scores) are used or when more precise location of lesion is not considered (e.g., lobe versus hemisphere-by-lobe effects). When specific subtest scores are used and/or more precise lesions are considered relative to brain volume loss, lesion location assumes a larger role. In this case, lesion location effects appear more pronounced in patients with left hemisphere involvement (and particularly left temporal or occipital lobe involvement).

Finally, as a follow-up to this finding that lesion location assumes a larger role relative to subtest performance, we used a multiple regression analysis on all unilateral lesion cases, using the AFQT subtests (recorded as proportion correct of items completed) as dependent variables. The brain was divided into 63 pairs of structures on the right and left which were coded for involvement on CT scans.

TABLE 8 POSTINJURY SUBTEST SCORE RATIOS* BY SELECTED LOBE EFFECTS[1] AND LESION GROUP MEANS*

| | | *Selected lobe effects* | | | | | |
|---|---|---|---|---|---|---|---|
| *Lesion group* | | *Frontal only* | *Temporal only* | *Parietal only* | *Occipital only* | *Frontal temporal* | *Parietal occipital* |
| All head-injured | n | 47 | 24 | 31 | 10 | 10 | 16 |
| Vocabulary | | 0.84 | 0.79 | 0.88 | 0.75 | 0.81 | 0.92 |
| Arithmetic | | 0.75 | 0.70 | 0.76 | 0.70 | 0.80 | 0.74 |
| Objects | | 0.80 | 0.75 | 0.81 | 0.81 | 0.79 | 0.83 |
| Boxes | | 0.67 | 0.66 | 0.72 | 0.79 | 0.80 | 0.69 |
| All unilaterals | n | 37 | 13 | 28 | 9 | 10 | 15 |
| Vocabulary* | | 0.85 | 0.80 | 0.88 | 0.73 | 0.81 | 0.92 |
| Arithmetic | | 0.78 | 0.70 | 0.78 | 0.68 | 0.80 | 0.74 |
| Objects* | | 0.80 | 0.71 | 0.82 | 0.82 | 0.79 | 0.83 |
| Boxes | | 0.66 | 0.68 | 0.73 | 0.78 | 0.80 | 0.72 |
| Right hemisphere | n | 19 | 5 | 17 | 5 | 3 | 7 |
| Vocabulary | | 0.84 | 0.87 | 0.90 | 0.83 | 0.77 | 0.90 |
| Arithmetic | | 0.77 | 0.68 | 0.76 | 0.72 | 0.83 | 0.69 |
| Objects | | 0.78 | 0.78 | 0.84 | 0.82 | 0.86 | 0.80 |
| Boxes | | 0.57 | 0.66 | 0.70 | 0.76 | 0.81 | 0.65 |
| Left hemisphere | n | 18 | 8 | 11 | 4 | 7 | 8 |
| Vocabulary* | | 0.86 | 0.76 | 0.86 | 0.61 | 0.83 | 0.93 |
| Arithmetic | | 0.80 | 0.71 | 0.80 | 0.63 | 0.80 | 0.78 |
| Objects* | | 0.82 | 0.67 | 0.80 | 0.81 | 0.76 | 0.86 |
| Boxes | | 0.75 | 0.70 | 0.77 | 0.79 | 0.79 | 0.77 |
| Bilateral | n | 10 | 11 | 3 | 1 | — | 1 |
| Vocabulary | | 0.80 | 0.78 | 0.85 | 0.96 | — | 0.88 |
| Arithmetic | | 0.63 | 0.71 | 0.62 | 0.96 | — | 0.80 |
| Objects | | 0.80 | 0.79 | 0.72 | 0.72 | — | 0.84 |
| Boxes | | 0.72 | 0.63 | 0.59 | 0.96 | — | 0.28 |

[1] Total sample sizes are reduced due to inclusion of only 138 cases that had the specified selected lobe effects *Ratios for each subtest were defined as number of items correct divided by number of items attempted ANCOVA significance levels *$P \leq 0.05$ The 'Bilateral' and 'All head injured' groups are shown for descriptive purposes only and were not included in the ANCOVAs

These structures, together with total brain volume loss, were used as predictors in a multiple backward stepwise regression.

The regression results suggest that impairment of vocabulary performance was localized mostly in structures in the temporal and posterior areas on the left side of the brain. The 10 most relevant structures along with their incremental explained variance estimates ($r^2$) to the regression model include: (1) parahippocampal and lingual cortex ($r^2=0.048$), (2) left uncus ($r^2=0.030$), (3) right calcarine cortex ($r^2=0.026$), (4) left posterior limb of internal capsule ($r^2=0.025$), (5) left cuneus ($r^2=0.022$), (6) left posterior-superior temporal cortex ($r^2=0.021$), (7) left hippocampus ($r^2=0.019$), (8) left thalamus ($r^2=0.018$), (9) posterior corpus callosum ($r^2=0.017$), and (10) left lateral temporo-occipital cortex ($r^2=0.008$).

For the arithmetic subtest, the 10 most relevant structures along with their incremental explained variance estimates ($r^2$) to the regression model include: (1) left lateral occipital cortex ($r^2=0.051$), (2) right calcarine cortex ($r^2=0.049$), (3) right thalamus ($r^2 = 0.046$), (4) left hypothalamus ($r^2 = 0.024$), (5) left superior precuneus ($r^2 = 0.023$), (6) left anterior midfrontal gyrus ($r^2 = 0.022$), (7) midleft superior temporal gyrus ($r^2 = 0.016$), (8) anterior left middle temporal gyrus ($r^2 = 0.011$), (9) left external capsule complex ($r^2 = 0.005$), and (10) anterior half of left internal capsule ($r^2 = 0.004$).

For the object-function matching subtest, the 10 most relevant structures together with their incremental explained variance estimates ($r^2$) to the regression model include: (1) posterior half of left internal capsule ($r^2 = 0.071$), (2) posterior corpus callosum ($r^2 = 0.043$), (3) posterior limb of left internal capsule ($r^2 = 0.039$), (4) right midfrontal cortex ($r^2 = 0.026$), (5) right calcarine cortex ($r^2 = 0.026$), (6) left frontal operculum ($r^2 = 0.020$), (7) left superior frontal white matter ($r^2 = 0.020$), (8) posterior third of left superior temporal gyrus ($r^2 = 0.017$), (9) mesial left superior frontal gyrus ($r^2 = 0.016$), and (10) left superior precuneus ($r^2 = 0.012$).

For the boxes subtest, the 10 most relevant structures, along with their incremental explained variance estimates ($r^2$) to the regression model, include: (1) right superior parietal cortex ($r^2 = 0.077$), (2) right anterior frontal cortex ($r^2 = 0.037$), (3) right thalamus ($r^2 = 0.023$), (4) right anterior inferior frontal cortex ($r^2 = 0.022$), (5) right superior paracentral lobule ($r^2 = 0.019$), (6) right cuneus ($r^2 = 0.017$), (7) left superior precuneus ($r^2 = 0.017$), (8) right middle temporal gyrus ($r^2 = 0.016$), (9) head of right caudate nucleus ($r^2 = 0.013$), and (10) right lentiform nucleus ($r^2 = 0.010$).

### *Other variables*

In our population, 33 of 38 head-injured patients classified clinically into a classical aphasic category (e.g., Broca's, Wernicke's, conduction, or transcortical sensory or motor) fell into the lower 40% of patients on the postinjury AFQT percentile score distribution (they were not included in our analyses). However, although a patient may not be classified as clinically aphasic, more subtle deficits in language abilities may persist which could adversely affect task performance. To explore this possibility, a patient was classified as having a reading disorder if he attained a score less than 95 (out of a possible 100 items) on the Reading Token Test, a score less than 40 (out of 42 sentences) on the Selnes Reading Comprehension/Receptive Syntax Test, or committed more than 10 errors (reading errors of any type) on the Gates-McKillop Reading Test and with the clinical consensus of three neurolinguists. If a patient score fell below 35 (out of 42 items) on an abbreviated version of the Boston Naming Test, he was identified as having a naming disorder (*see* Ludlow *et al.*, 1986, for a description of these tests). Using these criteria it was found that at least 50% of the patients have persistent mild reading or naming disorders. Moreover, performance on reading and naming tasks were highly correlated with post-AFQT score (*see* Table 2). Naming and reading comprehension skills are of obvious importance for successful test performance. Thus it is likely that penetrating wounds that involve the dominant hemisphere, and in turn language processes, may be responsible for a significant proportion of the variance in performance on the postinjury AFQT subtests and total score, even in clinically nonaphasic patients.

Correlational analysis also showed significant relationships between pre- to postinjury AFQT difference score and the following injury severity variables: total brain volume loss ($r = -0.42$, $P < 0.0001$), loss of consciousness ($r = -0.23$, $P < 0.0001$), presence of hemianopia ($r = -0.16$, $P < 0.01$), and presence of paresis ($r = -0.23$, $P < 0.001$). Other variables considered were nonsignificant, namely the degree of alcohol, illegal substance abuse, or presence of epileptic seizures (Table 2).

## DISCUSSION

Our results show that there are several factors that influence persistence of cognitive deficit following brain injury as measured by performance on an intelligence-type test. Foremost among them is the preinjury status of the patient as estimated by the preinjury AFQT percentile score. We found a 'regression to the mean' effect such that those brain-injured patients with higher preinjury AFQT scores were most likely to have a lowering of their postinjury scores, but these losses were generally within quintile categories and did not represent a substantial loss in overall cognitive performance. Similarly, in the case of those patients in the lower quintiles on preinjury testing and thus showing gains on postinjury testing, the gains were less than those demonstrated by the control group and did not represent a substantial improvement in cognitive performance. Controls also showed a regression to the mean effect, but their D-AFQT distribution is shifted up by approximately 10 points. These findings demonstrate that preinjury intelligence in brain-injured patients profoundly determines their level of postinjury intellectual recovery. These findings are further evidence for the relative stability of the overall AFQT (and possibly also the WAIS IQ; Grafman *et al.*, 1986), even after a 15 yr pre- to posttest interval coupled with a severe penetrating head injury.

Our results tentatively support part of Harlow's (1949) thesis that preinjury experience (in the form of education) is significantly associated with postinjury intellectual performance, *but only in subjects with preinjury AFQT scores below the 50th percentile*. This indicates that, given a lower level of intellectual ability, 'motivation' and persistence in learning as represented by higher educational attainment before injury, may have a positive affect on postinjury intellectual recovery. Teuber (1960) has commented on the premorbid personality of the brain-injured patient and its effect on postinjury behavioural recovery. He speculated that some of the very same structures that subserve intellectual abilities also subserve motivational processes (e.g., the frontal lobes). Thus both could be affected by a single brain injury or each could be independently affected. Whether, in fact, it is a preinjury enriched environment as represented by preinjury educational or intelligence level, the continued postinjury exposure to similar enriching conditions, or a continuing motivation to learn that 'protects' intellectual ability, is unknown. However, we found that the presence of a left hemisphere lesion and probable mild linguistic deficits markedly decreases the positive effect of higher preinjury intellectual/educational achievement on postinjury intellectual performance (*see also* Weinstein, 1962). These findings support our earlier results (Grafman *et al.*, 1986) and overlap with Teuber's results (Teuber, 1959) on the effects of lesion location, but dispute some of his conclusions on the lack of effect of preinjury experience.

When the effects of pretest performance were taken into account, total brain volume loss and lesion location were the most important predictors of performance. Patients with larger volume loss did significantly less well on the overall measure of intelligence (the AFQT percentile score). However, when specific subtest scores were considered, lesion location assumed a larger role relative to brain volume loss. In this case, lesion location effects appeared more pronounced in patients with left hemisphere involvement (e.g., patients with left temporal or occipital lesions did less well than other brain-injured groups on the vocabulary subtest of the AFQT).

Although clinically diagnosed aphasics were eliminated from this study (*see* Ludlow *et al.*, 1986, for a description of the VHIS neurolinguistic examination), patients with subclinical problems (i.e., mildly lowered reading comprehension or naming scores) were included and tended to do worse than other patients. This both reflects the invariable effect of left hemisphere brain damage on even subtle linguistic processes and the sensitivity of the AFQT to left hemisphere brain damage and, in turn, reduced language ability. This language bias in the AFQT is not unique for intelligence tests and reaffirms the bias towards basic language skills inherent in most tests of intelligence (e.g., the Wechsler Adult Intelligence Scale). The subtest least influenced by language skills in the AFQT is presumably the boxes subtest and on that test we noted the more disturbing effects of right hemisphere damage on performance. Therefore, even when overall intellectual ability, as indexed by a single score (e.g., total AFQT, full scale IQ), appears to remain relatively unaffected 15 yrs following penetrating brain injury, more specific cognitive and mood dysfunction will certainly result (Grafman *et al.*, 1985, 1986; Salazar *et al.*, 1986*a*, *b*).

The question thus arises as to the theoretical significance, if any, of the summary score, specifically, whether or not it indexes something other than the individual subtest components. In this regard, it is important to note that our findings were perfectly consistent with a model of mind that assumes only a modular organization, as well as with a model which includes a notion of general intelligence not completely reducible to separate cognitive faculties. Within the present framework, further delineation of this complex issue would require, at mimimum, analysis of pre- to postinjury changes on specific cognitive subtests.

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# REMOTE MEMORY FUNCTION IN ALZHEIMER'S DISEASE AND PARKINSON'S DISEASE

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## SUMMARY

Remote memory for public and personal events was evaluated in Alzheimer's disease (AD) and Parkinson's disease (PD), using a series of recall and recognition tests Information related to content and date of past events was assessed separately. In recall of the content of personal and public events, both groups showed a gradient of deficit in which remote events were affected less than recent ones; the magnitude and temporal extent of the retrograde loss was related to severity of dementia. By contrast, gradient effects were not evident in the recall of date and were less marked in the recognition of content or date. In public and personal events tests, patients with PD showed a relative impairment in dating capacity, compared with their memory for the content of events, which was independent of dementia. These results suggest that dementia affects the recall of distant events less than recall of recent ones. Furthermore, the selective gradient effects in recall of content suggest that memory for date is served by cognitive processes independent of memory for event content In PD, dating capacity is a sensitive measure of remote memory function that may be disrupted independently of dementia.

## INTRODUCTION

Studies of remote memory function in amnesia and dementia have attempted to define qualitatively different patterns of deficit based on the site and nature of the pathology in order to identify brain regions serving component processes involved in memory for past events. Particular attention has been devoted to processes that are concerned with the age of the memory and the nature of the recalled information. Thus, in amnesic syndromes, some authors (e.g. Squire and Cohen, 1984) have distinguished two groups of patients based on the temporal extent of the retrograde loss: one group, including the patient H.M. (Marslen-Wilson and Teuber, 1975; Corkin *et al.*, 1983; Sagar *et al.*, 1985*a*) showed a retrograde loss that involved the immediate premorbid period but spared more remote memories.

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The other group, including patients with Korsakoff's syndrome, showed a remote memory impairment that extended across several decades (Sanders and Warrington, 1971; Seltzer and Benson, 1974; Marslen-Wilson and Teuber, 1975; Albert *et al.*, 1979; Meudell *et al.*, 1980; Cohen and Squire, 1981). These results have been interpreted as reflecting differences among amnesic syndromes of different aetiology in the memory processes that are affected by the cerebral lesion. This distinction has not been supported by other investigators who have drawn attention to methodological problems in remote memory studies and who found no difference among amnesic syndromes in the temporal extent of retrograde loss using carefully selected test items (Sanders and Warrington, 1971, 1975). In dementia, all studies to date have shown a temporally-extensive deficit in remote memory function (Albert *et al.*, 1981*a*, *b*; Wilson *et al.*, 1981), similar to the pattern of decline in normal ageing (Warrington and Sanders, 1971).

Other distinctions in performance pattern in amnesia and dementia have been based on the nature of the recalled information. In normal subjects, Tulving (1972) proposed that memory comprises at least two component systems dealing with different classes of information: episodic memory and semantic memory. By this view, later elaborated from studies of amnesia by Kinsbourne and Wood (1975), episodic memory is concerned with autobiographical events defined by specific temporal and spatial context, whereas semantic memory involves rules, language and world knowledge poorly defined by time and place. Amnesia has been considered to comprise loss of episodic memory with preservation of semantic memory (Kinsbourne and Wood, 1975, 1982; Parkin, 1982; Schacter and Tulving, 1982*a*,*b*; Warrington and Weiskrantz, 1982; Wood *et al.*, 1982). The episodic/semantic distinction has highlighted factors that may reflect the functions of important component processes of memory, namely autobiographical and nonautobiographical reference, information related to single or multiple learning episodes, and information concerned with the content and temporal context of past events. It is not, however, clear that those processes are obligatorily associated in a way that is implied by the episodic/semantic distinction. Furthermore, the episodic/semantic distinction in memory processing may be too simplistic; for example, dissociations based on the nature of the recalled information have been found even within the realm of purely semantic material (Warrington, 1979; Warrington and Shallice, 1984).

In dementia, few studies have analysed remote memory function according to the nature of the recalled information, although deficits in both episodic and semantic systems are reported (Weingartner *et al.*, 1981, 1983). The patterns of remote memory deficit in dementias of different aetiology or in a single disease at different stages of progression may, however, differ according to the neural or neurotransmitter systems that are disrupted. In an attempt to further our understanding of cognitive processes involved in memory for past events, we have examined remote memory function in AD, PD and amnesic syndromes of mixed aetiology using tests that examine the nature of the recalled information and the age of the memory. Preliminary results of these studies have been presented previously (Corkin *et al.*, 1983; Sagar *et al.*, 1984, 1985*a,b*). This report provides detailed results comparing patients with AD and PD. The findings in amnesia will be reported separately.

## METHODS

### *Subjects*

The subject groups comprised 32 patients with Alzheimer's disease (AD), 23 patients with Parkinson's disease (PD) and 37 healthy control subjects (Table 1). The patients with AD were drawn from the Memory Disorders Unit at the Massachusetts General Hospital and were diagnosed according to strict inclusion and exclusion criteria (McKhann *et al.*, 1984; Khachaturian, 1985). None of the AD patients was taking psychotropic medication. The patients with PD were ambulatory patients attending the Movement Disorders Unit at the same hospital. They were selected randomly from consecutive clinic sessions independently of any behavioural criterion or treatment regime. The normal control subjects consisted of spouses (n = 26) or siblings (n = 3) of patients, patients with traumatic peripheral nerve injury (but no head injury) (n = 7) and nonacademic MIT personnel (n = 1).

TABLE 1. CHARACTERISTICS OF SUBJECT GROUPS: MEANS AND (BRACKETED) RANGE

| *Group* | *n* | *Age (yrs)* | *Education (yrs)* | *Duration* of disease (yrs)* | *Blessed Dementia Scale score*** |
|---|---|---|---|---|---|
| Control | | 62.2 | 14.0 | Not | 0.31 |
| | 17M, 20F | (53–78) | (10–20) | Applicable | (0–2) |
| Parkinson | | 64.0 | 14.6 | 7.9 | 3.48 |
| | 20M, 3F | (44–85) | (8–20) | (1–19) | (0–12) |
| Alzheimer | | 64.8 | 13.8 | 4.4 | 10.94 |
| | 12M, 20F | (54–77) | (8–22) | (2–14) | (1–27) |

* Memory and orientation section. ** Derived from retrospective history of onset of cognitive decline, not from time of presentation. n = number of subjects. M = male, F = female.

The groups were matched for age and years of education but the PD group had a significantly longer duration of illness ($P < 0.05$). Despite this difference, the PD patients were significantly less demented than the AD patients, as judged by performance on the memory and orientation section of the Blessed Dementia Scale (BDS) (Blessed *et al.*, 1968) ($P < 0.001$). Three patients with PD were demented by DSM-III criteria but a further seven cases, who did not fulfil these criteria, scored outside the control range on the BDS. Two of the patients with AD achieved normal scores on the BDS at the time of this study but showed impaired performance when retested 6 months later as the disease had progressed. The AD and control groups were sex matched but the PD group had a higher proportion of males than the other two groups.

Informed consent for neuropsychological testing was obtained from all subjects.

### *Public events*

Tests of public events comprised the Famous Scenes Tests and the Verbal Multiple Choice Recognition Test. The Famous Scenes Tests were given first in the order Yes/no Recognition, Recall and Multiple Choice Recognition. The Verbal Multiple Choice Recognition Test (Squire and Cohen, 1982) was given subsequently. Some subjects did not take the Recall Test but did take the remaining tests in the order noted above.

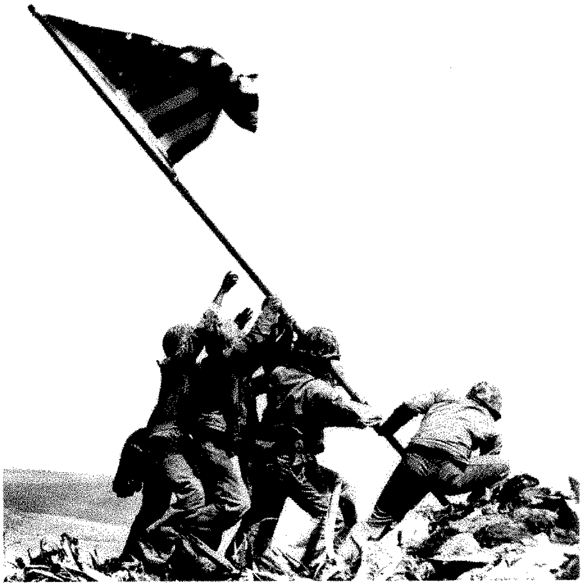
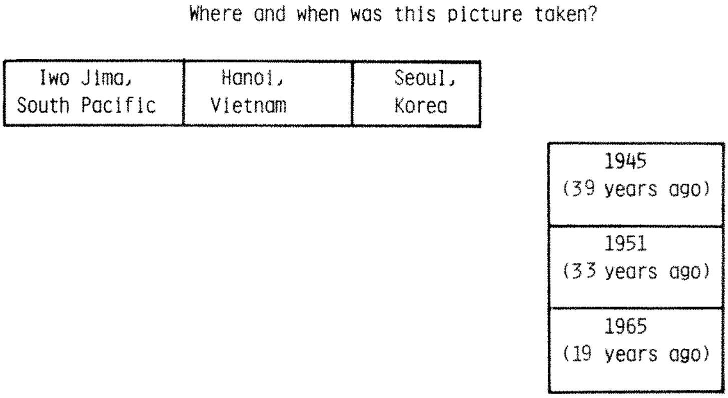


FIG. 1. An item from the Famous Scenes Test showing the raising of the flag on Iwo Jima after the US capture of the island from the Japanese in 1945.



Where and when was this picture taken?

| | | |
|---|---|---|
| Iwo Jima,<br>South Pacific | Hanoi,<br>Vietnam | Seoul,<br>Korea |

| |
|---|
| 1945<br>(39 years ago) |
| 1951<br>(33 years ago) |
| 1965<br>(19 years ago) |

FIG. 2. An example from the Famous Scenes Multiple Choice Recognition Test corresponding to the stimulus item shown in fig. 1.

*Famous Scenes Tests*

Subjects were shown news photographs depicting famous public events from the 1940s to the 1980s. Each event had occurred at a specific time and place which could not be deduced from the picture alone, for example, the raising of the American flag on Iwo Jima after the gain of the island from the Japanese in 1945 (fig. 1), or the shooting of Lee Harvey Oswald in police custody after his arrest for the assassination of President John F. Kennedy in 1963. Four photographs from each of the five decades were used in tests of yes/no recognition, recall, and multiple-choice recognition (Form I). Subjects sat in a quiet darkened room at a desk equipped with a reading lamp, and viewed the photographs projected onto a screen from a distance of approximately 10 feet.

*Yes/no recognition.* The 20 famous photographs of Form I were mixed with 16 nonfamous photographs, as foils, and presented in random sequence. Before the test, subjects were told that they would view a series of famous and nonfamous photographs, some of which they had seen in newspapers or magazines, and that they would be asked questions about each photograph. Upon presentation of each picture, they were asked 'Have you seen this picture before; does this picture seem familiar to you?' and were required to answer 'yes' or 'no'. Subjects were then presented with the appropriate recall or multiple choice recognition questions before presentation of the next photograph.

*Recall test.* This test was constructed in order to examine recall of different aspects of knowledge. Information related to each picture was divided into four categories for scoring purposes: event, content, scenario and date. Event-related information comprised those facts pertaining exclusively to the event depicted in the picture. Such information could not be deduced entirely from the scene but demanded knowledge of relevant, time-specific, historical facts. In the scene depicting the raising of the flag on Iwo Jima in 1945, for example, event-related information included Iwo Jima and the South Pacific war with the Japanese. Content referred to those items that were independent of any particular event and that could be identified by direct observation of the picture using inference from general world-knowledge. In the Iwo Jima example, these items included American soldiers and the American flag. Scenario defined the action of the picture as deduced from the elements of the scene. Such information, like content, was poorly defined by time and place and used world-knowledge in its reconstruction. In the scene of Iwo Jima, the scenario was the raising of the flag as a sign of victory; an incorrect interpretation, often made by patients with AD, was the taking down of the flag for transfer elsewhere. Dating information was concerned with the year from which the picture was drawn and hence the year in which the event took place. Thus, because content and scenario were not linked to specific events, they carried only loose temporal associations, whereas event-related information and date were highly specific to time. Each picture was analysed in this way; points were allocated to separate facets of information to give a maximum score within each category for each picture. For dating information, maximum score was set at 15 so that dating capacity could be quantitated by deduction of an error score in which one point corresponded to each year's inaccuracy over a ± 15 year period. All such analysis was finalized during construction of the test and before testing of patients.

During test administration, subjects were given 1 min to relate as much as possible about the content and action of each picture and about the event it represented. They were then asked questions to probe for the specific information within each category of event, content and scenario. Finally, they were asked to estimate the date when the picture was taken. All subjects' responses were tape-recorded, transcribed and scored for correct recall within each category of information. For event, content and scenario, results were calculated as the percentage of the maximum score and averaged across the four pictures of each decade. For dating, one point was deducted from the maximum score of 15 for every year's inaccuracy to a minimum of zero, and results were similarly expressed as the percentage of the maximum score.

*Multiple-choice recognition.* The Multiple Choice Recognition Test had a three-choice format, comprising the correct response and two incorrect alternatives (fig. 2). The foils represented other real-life events that had occurred approximately 5 and 15 yrs before or after the event depicted in the picture. The foil events were chosen so that they were equally distributed in time around the target event. Thus, for the four target events of each decade, two 5 yr and two 15 yr foil events predated the targets and two 5 yr and two 15 yr foil events postdated the targets. Recognition of content and date was assessed using separate but simultaneous choice displays. The content items were displayed horizontally and the dating items vertically. The order of display was randomized separately for content and date. Subjects viewed the recognition questions by a reading lamp while the corresponding picture was projected onto a screen. They were instructed to make one choice within each category and to mark their answers on the question sheet. A separate sheet was used for each question and the test instructions were repeated with the presentation of each stimulus item. There were two forms of this test, each consisting of 20 pictures, 4 per decade.

### *Verbal Multiple-Choice Recognition Test*

Subjects read silently 30 questions concerning details of public events from the 1940s to the 1970s (Squire and Cohen, 1982). Questions were presented one at a time, each on a separate sheet, and responses were obtained using a 4-choice recognition format. Subjects marked their choice on the question sheet. If subjects had difficulty in performing the task, the instructions were repeated or the questions were read aloud by the examiner while the subject viewed the question sheet.

## *Personal events*

### *Modified Crovitz Personal Remote Memory Test*

In this modification of Crovitz and Schiffman's (1974) test, subjects were asked to relate personally-experienced events from any remote time period involving each of 10 high-frequency noun cues: bird, flag, tree, car, ship, boy, arm, star, clock, table. Subjects were given up to 4 min to respond, including, if necessary, 2 min with specific cues. If, within the first 2 min patients responded incompletely or not at all, the examiner prompted them with nonspecific cues (e.g., 'Tell me more;' 'Can you think of one instance?'). Responses were scored on a 0 to 3-point scale, depending upon the degree of specificity to time and place of the memory recalled (Zola-Morgan *et al.*, 1983). A score of 3 was given for a memory with autobiographical involvement, a specific instantiation of the stimulus cue, specificity to time and place and richness of detail (e.g., 'I bought a chiming onyx clock for my wife's birthday for $50 from Harper's in New York'). A score of 2 was given for an autobiographical memory with specific instantiation of the stimulus cue but characterized by a lack of temporospatial specificity or by marked poverty of detail (e.g., 'I used to climb a big oak tree on the edge of a forest near my parents' house;' 'I once took a cruise to somewhere in Europe'). A score of 1 was given for a memory with autobiographical content but no instantiation of the stimulus cue or specificity (e.g., 'I used to enjoy bird-watching'). A score of 0 was given for no response or a general statement with no autobiographical reference (e.g., 'Birds fly around').

If subjects achieved a score of 2 or 3 within the first 2 min, the second 2 min were used, if necessary, for amplification of detail, e.g., 'In what store did you buy the clock?' 'How much did it cost?'. Subjects who achieved a score of 0 or 1 in the first 2 min were given a further 2 min with cues consisting of examples of specific memories, e.g., 'Have you ever seen an unusual bird?' 'Have you ever bought a table?' but avoiding examples restricted to particular time periods. Subjects were then asked to date memories that earned a score of 3. Finally, after all 10 nouns had been given, subjects were required, without warning, to recall them (i.e., bird, . . ., table).

The following day, again without warning, a second recall test of the word list was given. Each cue word was then presented again and subjects were required to reproduce the previous day's memory. Responses were scored on the same 0 to 3-point scale for memories that were wholly or in part reproduced on Day 2; the score on Day 2 could not exceed that on Day 1. Subjects were again given 2 min to respond. If they failed to regain their Day 1 score after 2 min, they were cued with key words from their Day 1 memories (e.g., 'Onyx') and were given a further 2 min to respond. Subjects were again asked to date memories that earned a score of 3. Finally, on Day 2, subjects were given a third trial of recall of the 10-word list.

## RESULTS

Not all tests were taken by all subjects but, for each test, the participants were a random selection of each subject group. The number of participants in each test is shown on the accompanying figures.

## *Statistical methods*

The distributions of data points for the remote memory tests did not always conform to a normal distribution and variances were not homogeneous between data sets. Some measurements followed only an ordinal scale. Nonparametric statistics were therefore used throughout. Unless otherwise stated, differences among three or more populations of data were evaluated by the Kruskal-Wallis one-way analysis of variance (statistic H), or, when samples were related, by the Friedman two-way analysis of variance (X). Paired comparisons were made post hoc using the Mann-Whitney two-tailed test (U or Z).

### *Public events tests*

#### *Famous Scenes Tests*

No discernible differences emerged on any segment of this test that were related to the sex or age of the patients, duration of disease or nature of drug treatment.

*Yes/no recognition.* Compared with control subjects, patients with AD made as many false positive responses to the novel pictures but claimed to have seen fewer of the famous pictures ($P<0.001$). This deficit in yes/no picture recognition affected recent and remote time periods, affecting stimuli drawn from the 1980s, 1960s and 1940s.

Patients with PD did not differ from control subjects in the number of false positive responses or in overall picture recognition but did show differences when recognition was analysed according to the decades from which the pictures were drawn. Paired comparisons showed PD patients to be defective in recognition of pictures from the 1980s but not the more remote decades ($P<0.02$).

*Recall.* Recall test scores were analysed statistically as total scores and the distribution of scores across decades. Recall scores of information related to event, content/scenario and date were evaluated separately.

On *total scores*, patients with PD and patients with AD were impaired in recall of all classes of information and could not be distinguished from each other, despite a significant difference ($P<0.02$) in BDS score (for AD vs control, event, content/scenario and date, $P<0.01$; for PD vs control, event and date, $P<0.01$, content/scenario $P<0.05$). In order to take account of item difficulty, the raw scores for each picture were ranked across subject groups and a sum of ranks for each group was obtained by adding together the ranks for each picture. Using this analysis, patients with PD remained impaired in recall of event ($P<0.05$) and dating ($P<0.01$) information but not of content/scenario information. AD patients were impaired on all measures ($P<0.01$) and PD and AD patients could not be distinguished on any measure.

An *analysis of the results by decade* showed that the distribution of the deficits across decades differed according to the nature of the recalled information (fig. 3). For event-related information, AD and PD patients showed a temporal gradient of deficit, more recent decades being the more severely affected in both groups (for PD, $X=12.2$, $P<0.02$; for AD, $X=10.8$, $P<0.05$). The two groups differed, however, in the temporal extent of the loss. Relative to control subjects, AD

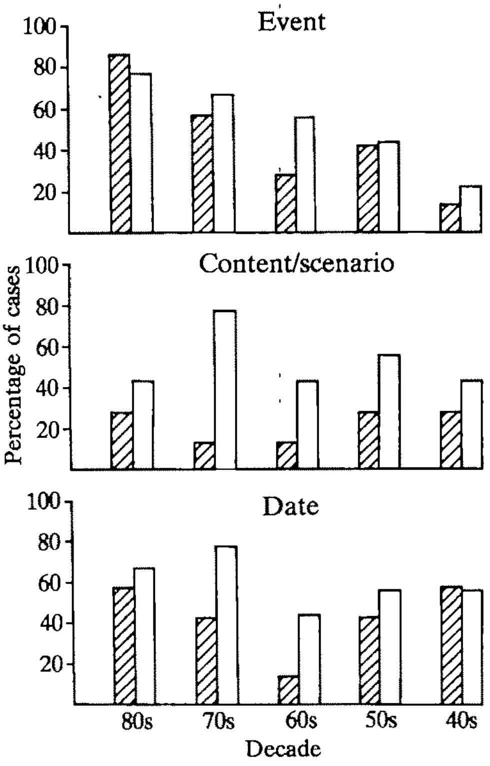


FIG. 3 Percentage of subjects in each patient group with scores below the normal range in the Famous Scenes Recall Test. Results are shown for each class of information according to the decade from which the scenes were taken. For event-related information, but not content/scenario or date, there was a gradient of deficit in which remote memories were relatively spared PD (hatched areas) n = 7, AD (open areas) n = 9

patients showed an extensive loss across all five decades ($P<0.02$) but PD patients had a deficit that was significant only for the 1980s ($P<0.002$) and 1970s ($P<0.05$). For information concerning content and scenario, the deficit of AD patients differed across decades ($X=14.5$, $P<0.01$), the lowest scores relating to events from the 1960s. This temporal pattern was similar but less marked in patients with PD, and represented an exaggeration of the distribution of performance across decades in control subjects. For dating information, PD and AD groups showed no temporal gradient. The deficits were temporally-extensive, affecting decades from the 1940s to the 1980s (for PD, 40s, 50s, 60s, $P<0.05$; 80s, $P<0.01$; for AD, 40s, 50s, 60s, 70s, $P<0.01$; 80s, $P<0.05$), and did not differ between the two groups.

Fig. 4 shows the results analysed according to the severity of dementia. Based on the BDS, the PD group was split into 2 subgroups: Group I with normal BDS score (0–2) and Group II with BDS scores (3–12) outside the control range. The AD group was divided into 2 subgroups of equal size, one mildly demented (BDS 7–9) and the other moderately demented (BDS = 10–15). (One early AD patient with a BDS score of 2, 6 months later rising to 5, is excluded from this analysis. He scored normally at all decades.) For event-related information, all groups showed a temporal gradient of deficit, with the more recent decades most severely affected, but the temporal extent of loss varied according to the severity of dementia.

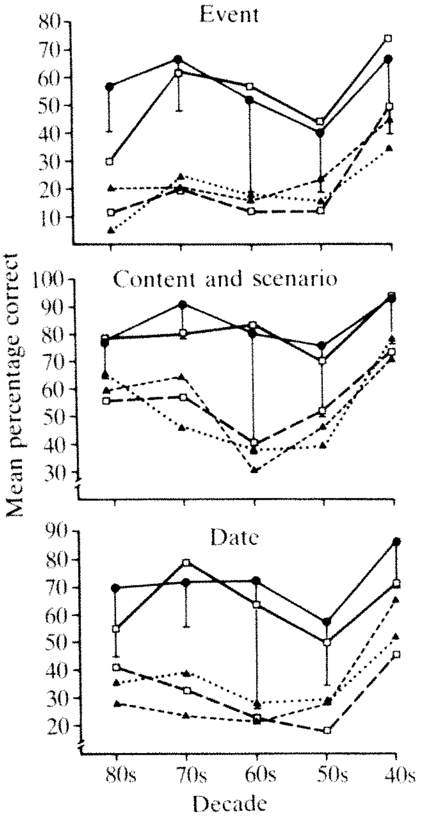


FIG. 4. Mean performance by decade on the Famous Scenes Recall Test related to severity of dementia, as assessed on the Blessed Dementia Scale (BDS). The range of BDS scores for PD Group I was 0–2; for PD Group II, 3–12; for mild AD, 7–9; and for moderate AD, 10–15. Recall scores for all classes of information were poorer in the more demented patients. The temporal extent of the deficit was related to dementia severity for event-related information but not for content/scenario or date. ●—● = control (n = 11), □—□ = PD Group I (n = 3), □---□ = PD Group II (n = 4), ▲---▲ = mild AD (n = 4), ▲...▲ = moderate AD (n = 4). Vertical lines = lower limit of normal range.

Moderately demented AD patients had a mean score that was outside the range of control subjects for all decades sampled. Mildly demented patients with AD and Group II patients with PD had mean scores within the range of control subjects for the 1940s but outside this range for, respectively, 3 or 4 of the remaining 4 decades. Group I PD patients had mean scores within the normal range for all decades except the 1980s for which their performance declined acutely. This pattern contrasts with the distribution of deficits in recall of dating information. The severity of deficit was related to the presence or absence of dementia but a significant temporal gradient was absent. There was no relationship between the temporal extent of the deficit and the duration of the disease, which in this sample was unrelated to the BDS.

*Multiple-choice recognition.* Recognition test scores were analysed as total scores, content-dating differences and the distribution of scores across decades.

For all subject groups, *total scores* indicated that dating recognition was more difficult than content recognition, as shown by the inferior mean score on the dating items compared with the content items (Table 2) ($P < 0.001$). The groups differed in total content recognition ($H = 22.6$, $P < 0.001$) and dating recognition ($P < 0.001$).

In overall performance, patients with AD were impaired relative to control subjects in recognition of both content and date ($P<0.001$). Patients with PD, by contrast, were impaired in recognition of date ($P<0.002$) but did not differ from control subjects in recognition of content. The performance of patients with PD in recognition of both content and date was superior to that of patients with AD ($P<0.001$ for both content and date).

Two cases of AD and 11 cases of PD whose BDS scores were in the 0 to 2 (normal) range scored normally on recognition of both content and dating (when retested on BDS 6 months later, the 2 AD cases scored in the demented range). Performance in the remaining 10 patients with PD and 25 patients with AD decreased with increasing BDS score (fig. 5).

For each subject, dating recognition was evaluated independently from content recognition by computation of the difference between the recognition scores of content and date which was known as the *content-dating recognition difference* (fig. 6). The total content-dating recognition difference was significantly less in the healthy control subjects than in either the patients with PD or the patients with AD, who did not differ from each other on this measure ($H=11.4$, $P<0.01$; in paired comparisons, $P<0.01$ control subjects vs AD and PD).

The differences in PD were, however, independent of the presence or absence of dementia as defined by the BDS. Both Group I (BDS 0–2) and Group II (BDS 3–12) patients with PD had content-dating recognition differences that were greater than those of control subjects and that did not differ from each other or from the scores of patients with AD (Group I PD vs control subjects, $P<0.005$; Group II PD vs control subjects, $P<0.01$).

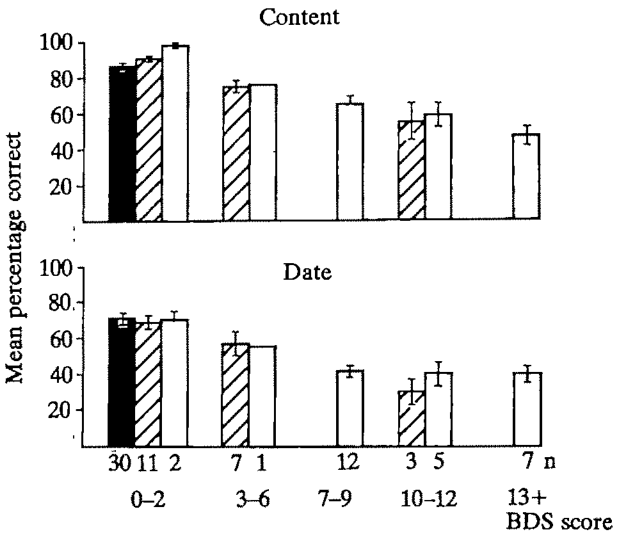


FIG 5. Total scores on the Famous Scenes Multiple Choice Recognition Test (Form 1) (mean ± SEM) related to severity of dementia as assessed by the BDS. Performance in both PD and AD declined with increasing BDS score Control (filled area), PD (hatched area), AD (open area).

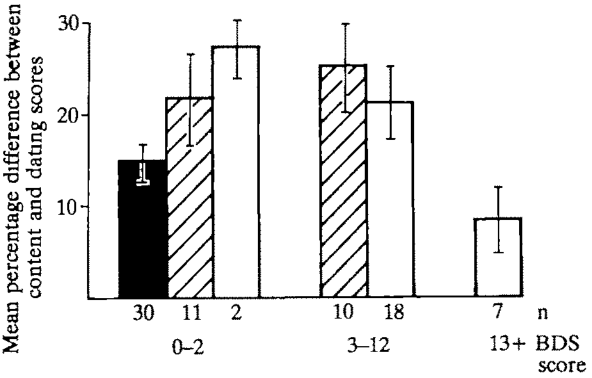


FIG. 6. Difference between scores on content recognition and dating recognition (mean ± SEM) in the Famous Scenes Multiple Choice Recognition Test (Form 1) related to severity of dementia as assessed by the BDS The PD group showed content-dating difference score greater than that of the control group and independent of BDS score. Key as in fig 5

*Analysis of the results by decade* (fig. 7) showed that the impairment in content and dating recognition in AD was temporally-extensive: compared with control subjects, patients with AD were impaired in recognition of content and date for events from all decades examined, from the 1940s to 1980s ($P<0.01$). Similarly, the impairment in dating recognition in PD was temporally-extensive, involving the 1980s, 1970s and 1940s ($P<0.01$); the differences for the 1950s and 1960s were not significant.

### *Verbal Multiple-choice Recognition Test*

The pattern of performance on this test was similar to the content recognition in the Famous Scenes Test. Patients with AD showed deficits compared with control subjects, whereas patients with PD performed normally. The impairment in AD was temporally-extensive, affecting all decades from the 1940s to the 1970s (for 40s, $P=0.01$; for 50s, 60s, 70s, $P<0.002$) (fig. 8).

## *Personal events tests*

### *Modified Crovitz Test: recall of personal memories*

As in the public events tests, the results were not related to differences in sex, age, disease duration or treatment regime.

The *total scores* of healthy control subjects and patients with PD or AD on the Modified Crovitz Test for Days 1 and 2 with and without cues are shown in fig. 9. All subjects benefited from cues. There were differences, however, between subject groups in their cued ($H=28.8$, $P<0.001$) and uncued ($H=29.6$, $P<0.001$) scores on both days. Healthy control subjects achieved near perfect performance on Day 1, with or without cues, and were able fully to reproduce these memories on Day 2.

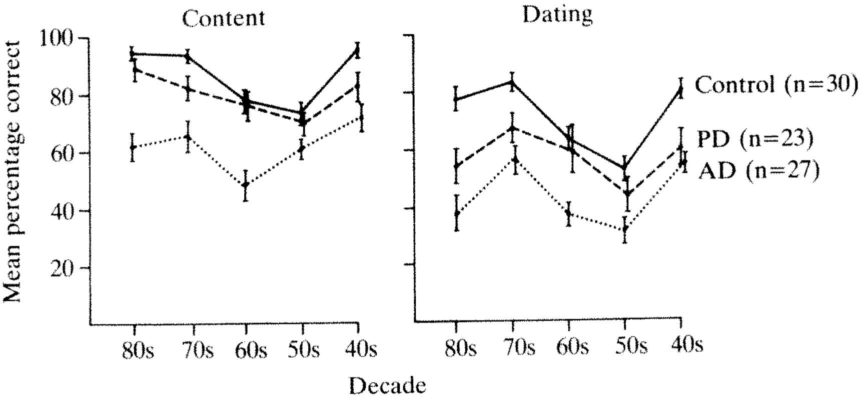


FIG. 7. Recognition of content and date according to decade in the Famous Scenes Recognition Test, Form 1 (mean ± SE). Unlike AD patients, PD patients showed selective impairment in dating recognition. Deficits in both patient groups were temporally-extensive.

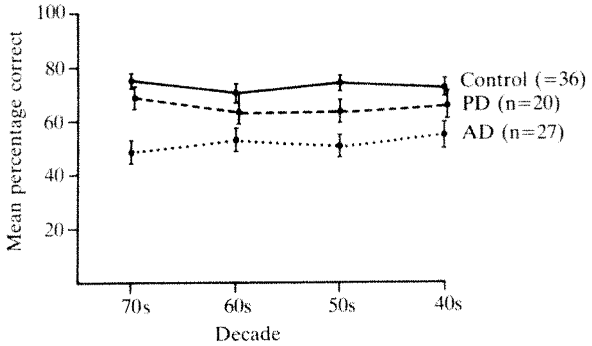


FIG. 8. Performance according to decade on the Verbal Multiple-Choice Recognition Test of Public Events (mean ± SEM). AD patients showed a temporally-extensive deficit but PD patients performed normally.

Patients with AD were impaired in recall of autobiographical episodes on Day 1, whether cued or uncued ($P < 0.001$), and showed a further deficit in reproduction of Day 1 memories on Day 2 ($P < 0.01$). AD patients with higher BDS scores achieved poorer performance on both days, with or without cues, than those with lower BDS scores (Table 2). The decline in scores from Day 1 to Day 2 also varied with the severity of dementia. On Day 2, some patients with AD were unable to match the uncued score of Day 1 even when cued with components of their own Day 1 memories. These subjects had higher BDS scores than those whose Day 2 scores with cues were at least as great as the Day 1 scores without cues ($P < 0.01$).

On Day 1, patients with PD were mildly impaired in recall of autobiographical episodes, with or without cues ($P < 0.025$). On Day 2, they showed a deficit in reproducing Day 1 memories ($P < 0.025$) but regained their Day 1 performance when cued. The cued and uncued scores of the patients with PD were higher on

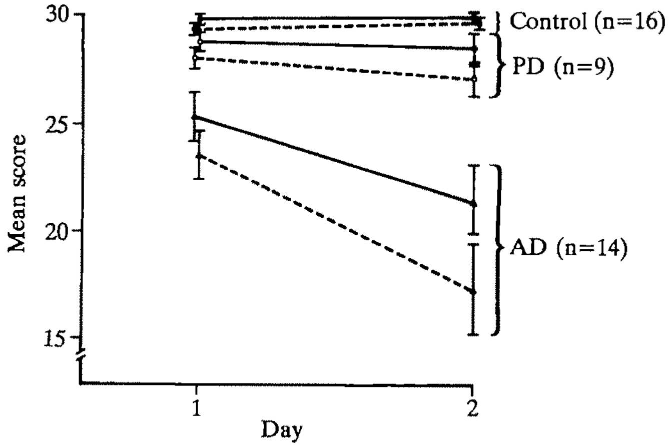


FIG. 9 Cued and uncued scores on Days 1 and 2 of the Modified Crovitz Personal Remote Memory Test only for subjects who were tested on both days (mean ± SEM) AD patients were impaired in cued and uncued scores on both days and showed a decline in performance from Day 1 to Day 2. PD patients were mildly impaired in cued and uncued scores on Day 1, on Day 2, they showed a decline in uncued scores but regained Day 1 performance with cues Cued (continuous line), uncued (broken line).

both days than the scores of patients with AD ($P < 0.001$). The Group II patients with PD (BDS 3–12) tended to perform more poorly on both days than the Group I patients with PD (BDS 0–2) (Table 2).

In both patient groups, impaired performance was characterized by a failure to recall time-specific events; patients were usually able to relate memories with autobiographical content and could often describe a specific instantiation of the stimulus word, but they tended to generalize across a number of recurrent similar episodes.

TABLE 2 CUED AND UNCUED SCORES ON DAYS 1 AND 2 OF THE MODIFIED CROVITZ PERSONAL REMOTE MEMORY TEST (MEAN ± SEM) FOR SUBJECTS GROUPED ACCORDING TO BDS SCORE

| | *Day 1* | | | *Day 2* | | |
|---|---|---|---|---|---|---|
| | *n* | *Uncued* | *Cued* | *n* | *Uncued* | *Cued* |
| Control | 20 | 29.1 | 29.5 | 15 | 29.4 | 29.6 |
| | | (1.25) | (0.83) | | (0.91) | (0.63) |
| PD | | | | | | |
| Group 1 | 11 | 28.6 | 29.0 | 4 | 28.5 | 29.3 |
| (BDS 0–2) | | (0.41) | (0.89) | | (0.65) | (0.48) |
| Group 2 | 6 | 26.7 | 27.8 | 5 | 26.2 | 27.6 |
| (BDS 3–12) | | (0.80) | (0.83) | | (1.19) | (0.93) |
| AD | | | | | | |
| Mild | 9 | 24.7 | 26.2 | 9 | 20.9 | 23.6 |
| (BDS 6–9) | | (0.60) | (0.52) | | (1.81) | (1.15) |
| Moderate/severe | 10 | 21.7 | 22.7 | 8 | 12.4 | 17.5 |
| (BDS 10–27) | | (2.09) | (1.97) | | (2.09) | (2.72) |

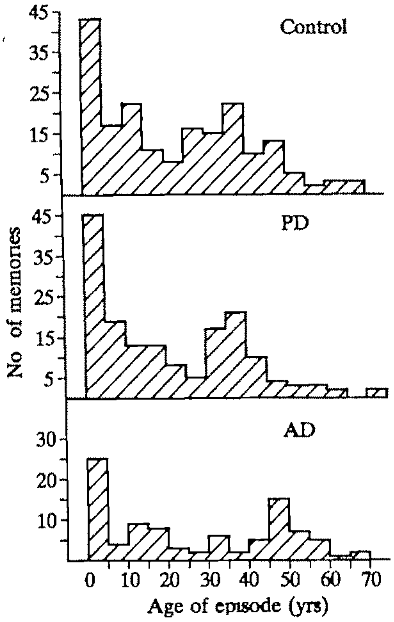


FIG. 10. Age distribution of episodes recalled in the Modified Crovitz Personal Remote Memory Test. In all groups, memories were drawn most readily from recent time periods but this was less marked in AD than the other two groups.

In the analysis of the age of episodes recalled (fig. 10), data were used only for specific memories that were consistently recalled on the two successive days. In all subject groups, memories were drawn most frequently from the most recent 5 yr period. The frequency of memories recalled from more remote time periods declined with increasing age of the memory so that the age distribution of memories conformed approximately to a forgetting curve in remote memory. Superimposed on this curve, however, the normal subjects and the patients with PD showed a second peak of frequency corresponding to the period 35–40 yrs ago (1943–1948). Patients with AD also showed a second peak but, unlike the pattern in the other two groups, this was shifted into the more remote time periods. In PD and AD groups, patients with higher BDS scores drew a greater proportion of their memories from the more remote time periods than did patients with lower BDS scores (Table 3).

*Consistency of dating* was evaluated from a comparison of the date estimates on Days 1 and 2 of those specific episodes that were recalled successfully on the two days. For each subject group, correlation coefficients were calculated between pairs of dates, using all specific memories produced by subjects within a group. On this measure, normal subjects showed consistency of dating across the two days ($r = 0.997$, $P < 0.001$). Patients with PD or AD also showed significant consistency (for PD, $r = 0.96$; for AD, $r = 0.92$; $P < 0.001$), but both groups were markedly impaired when compared with the virtually perfect performance of the control subjects (X across subject groups, $P < 0.001$; PD and AD vs controls, $P < 0.001$).

TABLE 3 NUMBER OF AUTOBIOGRAPHICAL EPISODES RECALLED FROM RECENT AND REMOTE TIME PERIODS*

| | | *Age of episode (yrs)* | | *Total no of memories* |
|---|---|---|---|---|
| | *n* | *0–35* | *36–70* | |
| Control | 20 | 132<br>(69.5%) | 58<br>(30.5%) | 190 |
| PD | | | | |
| Group I | 11 | 83<br>(83.0%) | 17<br>(17.0%) | 100 |
| Group II | 6 | 26<br>(54.2%) | 22<br>(45.8%) | 48 |
| Total | 19** | 120<br>(72.7%) | 45<br>(27.3%) | 165 |
| AD | | | | |
| BDS≤7 | 6 | 34<br>(70.8%) | 14<br>(29.2%) | 48 |
| BDS 8–16 | 9 | 22<br>(48.9%) | 23<br>(51.1%) | 45 |
| Total | 15 | 56<br>(60.2%) | 37<br>(39.8%) | 93 |

* The age distribution of recalled episodes differs between PD Group I and PD Group II ($P<0.001$) and between AD (BDS$\leqslant$7) and AD (BDS 8–16) ($P<0.05$). ** BDS unknown in 2 cases

In PD, dating consistency was impaired in both Group I ($r=0.978$) and Group II ($r=0.95$) patients ($P<0.001$ for difference from controls) who did not differ significantly from each other on this measure.

### *Modified Crovitz Test: Word-List Recall*

The subject groups differed on all three trials of recall of the cue words (Trial 1, H=36.9; Trial 2, H=25.5; Trial 3, H=29.8; $P<0.001$ in all cases). Patients with PD performed worse than healthy control subjects but better than patients with AD (for Trial 1, PD vs controls, $P<0.005$, PD vs AD, $P<0.002$; AD vs controls, $P<0.002$; for Trial 2, PD vs controls, $P<0.02$, PD vs AD, $P<0.02$, AD vs controls $P<0.002$; for Trial 3, PD vs controls, $P<0.002$, PD vs AD, $P<0.002$, AD vs controls, $P<0.002$). The performance of demented patients with PD was worse than that of nondemented patients with PD ($P<0.05$) whose scores did not differ from those of control subjects.

## DISCUSSION

In this study, we examined facets of remote memory function in patients with diffuse histological or neurochemical brain lesions. The design incorporated tests of recall and recognition of public events, recall of personal episodes, memory for the content and context of past events and the temporal distribution of memory loss. The results suggest dissociations in remote memory capacity related to the age of the memory, the nature of the recalled information and the aetiology of the memory disorder.

*Extent of retrograde loss and the temporal gradient*

This study has investigated the temporal pattern of remote memory deficit for personal and public events in AD and PD. In recall of personal events, normal patients showed a forgetting function across remote time periods so that more recent events were recalled more frequently. In the PD and AD groups, subjects with higher BDS scores recalled a greater proportion of their memories from the remote time periods than did patients with lower BDS scores. In recall of public events, analyses of variance also showed gradients of deficit in the two patient groups, the most recent memories being the most severely affected. In AD, the impairment was shown to be temporally extensive, spanning five decades, but, in PD, the deficits were significant only for the most recent decades. On recognition tests, there was no significant gradient across decades.

*Basis of the temporal gradient: biological or artificial?* In studies of amnesic syndromes, a distinction has been drawn between temporally-limited and temporally-extensive remote memory impairment (Squire and Cohen, 1984): Patient H.M. (Scoville and Milner, 1957; Marslen-Wilson and Teuber, 1975; Corkin *et al.*, 1983), patients treated with bilateral ECT (Squire *et al.*, 1975, 1976; Squire and Cohen, 1979; Cohen and Squire 1981), patients with closed head injury (Russell and Nathan, 1946) and some postencephalitic patients (Rose and Symonds, 1960) showed a retrograde amnesia confined to the immediate premorbid period, remote memories being spared. In contrast, patients with Korsakoff's syndrome (Seltzer and Benson, 1974; Marslen-Wilson and Teuber, 1975; Albert *et al.*, 1979; Mair *et al.*, 1979; Meudell *et al.*, 1980; Cohen and Squire, 1981), Huntington's disease (Albert *et al.*, 1981*a,b*), a mixed group of amnesic subjects (Sanders and Warrington, 1971, 1975) and the postencephalitic patient S.S. (Cermak and O'Connor, 1983) showed a remote memory loss that extended over several decades. Within the temporally-extensive loss, some patients with Korsakoff's syndrome (Seltzer and Benson, 1974; Marslen-Wilson and Teuber, 1975; Albert *et al.*, 1979; Cohen and Squire, 1981) and the patient S.S. (Cermak and O'Connor, 1983) showed a gradient in which recent memories were the more severely affected. Other cases of Korsakoff's syndrome (Sanders and Warrington, 1971; Mair *et al.*, 1979) or patients with medial temporal lobe pathology (Sanders and Warrington, 1971), Huntington's disease (Albert *et al.*, 1981*a,b*) or AD (Wilson *et al.*, 1981), showed equal involvement of all remote time periods.

The interpretation of these findings has differed among observers. Squire and Cohen (1984) have claimed that temporally-limited and temporally-extensive retrograde amnesia (RA) result from disruption of different memory processes. Others have drawn attention to the pitfalls inherent in test item selection (Sanders and Warrington, 1971, 1975; Weiskrantz, 1985). Two particular factors bias the results to produce erroneous temporally-limited RA or temporally-extensive RA with gradient. First, the items from different decades may differ in salience: selected events from the 1940s that have remained memorable in the 1980s may be inherently more important than selected events from the 1980s, some of which would be forgotten after an equivalent 40 yr delay. Secondly, some remote events may become more memorable as a result of repeated exposure, on television, in books and in magazines, whereas for recent events such exposure is necessarily less because of the briefer period that follows their occurrence. Some studies of amnesic patients have reported relative preservation of remote events even when account is taken of those methodological and ecological factors, such as memory for one-season TV programmes after bilateral ECT (Squire and Cohen, 1979) and acute loss of autobiographical memories in the Korsakoff patient P.Z. (Butters, 1984).

In our study, relative preservation of remote events in the more demented patients was shown for personal events as well as public events. In our public events tests, we used stimuli of high memorability so as to increase the sensitivity to residual knowledge in conditions of severe amnesia and dementia. Furthermore, we used pictures as stimuli because they invoke perceptual and inferential processes to analyse the scene and allow contextual features from the picture to develop a strong network of retrieval cues. These attributes render the test of particular value in analysing remote memory processes serving different aspects of information and the way that these processes may be differentially affected by disease. Such attributes, however, necessarily increase the memorability of the events. Thus, although of high temporal specificity, it is unlikely that the event-related information would fall rapidly from public awareness and the increased memorability thereby associated with the more remote items would contribute to the origin of a temporal gradient in results of the Famous Scenes Test. These criticisms do not, however, apply to the test of recall of personal events. Using this test, the proportion of memories recalled from the more remote time periods compared with the more recent time periods was greater in PD and AD subjects with higher BDS scores than in those with lower BDS scores. These observations, which imply preservation of more distant events in the remote memory deficits of dementia, support the results of the Famous Scenes Recall Test. Taken together, the results suggest that dementia has a greater effect on the recall of recent memories than of remote memories.

*Recall, recognition and the temporal gradient.* The temporal gradient of deficit in recall tasks shown by both patient groups was not evident in recognition tasks. Here, performance of both groups, whether normal or impaired, was equal across decades. The two types of memory test used the same stimuli and the subgroups of patients who took the recall task also took the recognition task with results qualitatively similar to the groups as a whole. The difference in the pattern of results between recall and recognition tasks cannot therefore be due to differences in test material or patient selection. Instead, the different patterns of performance may reflect involvement of different memory processes. Similar differences between recall and recognition tasks have been described in the postencephalitic patient

S.S. (Cermak and O'Connor, 1983) and attributed to a combination of retrieval and storage deficits. Material rendered inaccessible by disease is lost from all time periods equally and results in a 'flat' pattern of deficit in recognition tasks. The temporal gradient which, in AD and PD patients and the patient S.S., was evident only on recall tasks, suggests the presence of retrieval deficits that affect recent memories more than remote memories. These impairments are superimposed upon the normal forgetting that occurs in long-term memory and affects all class of material (Warrington and Sanders, 1971).

Although statistically the retrograde loss in recall tasks in PD was temporally-limited whilst that in AD was temporally-extensive, the two diseases were similar in the continuous nature of the retrograde gradient of deficit. Furthermore, the extent of retrograde loss in both diseases was linked to the severity of the dementia. Demented patients with PD showed impairment across several decades, whereas nondemented patients had deficits confined to the 1980s. These observations suggest that the effects of the dementing process on remote memory function are to cause loss of the most recent memories first and, as the condition advances, to affect increasingly remote memories in turn (Ribot's Law) (Ribot, 1882). In this way, an early gradient of deficit would be created in which recent memories were severely affected but remote memories were spared. Later, the involvement of the most remote memories would lead to a temporally-extensive deficit with gradient.

### *Memory for different classes of information*

The second goal of this study was to examine remote memory capacity for different aspects of information. The use of memorable, detailed and meaningful pictures in the Famous Scenes Test allowed us to examine memory for information that was strongly linked to the event in content or date as well as information that was independent of the event, but which could be reconstructed from world-knowledge. Not surprisingly, memory capacities for content and date were, in general, closely correlated. Dating capacity was highly sensitive to disruption of remote memory processes so that, in normal and patient groups, dating performance was consistently inferior to memory for event content of past events.

*Dating deficits: relationship to dementia.* Patients with AD were impaired in recall and recognition of content and date to a degree that correlated with severity of dementia. In PD, dating capacity proved a sensitive measure of remote memory capacity. Thus the Group I PD patients, who scored normally on the BDS, showed evidence of selective dating deficits in personal and public events tests. The content-dating difference score on the Famous Scenes Test was greater than that of control subjects and did not differ from the scores of patients with AD. Similarly, on the Crovitz Test, dating consistency from Day 1 to Day 2 was impaired relative to control subjects. This evidence of impaired dating capacity in the Group I PD patients occurred despite normal recognition of the content of past public events, normal ability to recall autobiographical episodes and normal ability to recall the Crovitz cue words on all three trials. The Group II PD patients showed dating performance that was, in general, no better than that of the AD group, despite superior scores on the BDS and on tests of memory for the content of past events. These results show that patients with PD may be selectively impaired in dating capacity and demonstrate that remote memory deficits may be present in PD subjects who are nondemented by clinical criteria or by scores on the minimental state examination.

*Dating deficits: cognitive processes.* Although dating capacity was inferior to event memory in both patient groups, the pattern of deficit across decades differed qualitatively for these two aspects of information. In PD and AD, a temporal gradient across decades was found for event-related information but not for content/scenario or date. Because event and content/scenario information differ considerably in their temporal specificity, qualitatively different patterns of loss across time would be expected. The differences between event-related information and dating information in temporal gradient effects cannot, however, be explained by differences in temporal specificity since both are related to the same events that occurred at specific points in time.

This qualitatively different pattern of performance across decades suggests that dating of past events may be served by cognitive processes separate from those concerned with memory for the content of past events. This finding, together with the observations of isolated dating deficits in some patients with Parkinson's disease, raises the possibility that processes serving dating capacity may be disrupted early and selectively in PD. Although dating is more difficult than recall or recognition of event content, some observations suggest that selective or disproportionate dating deficits in PD are not simply a consequence of differential task difficulty in patients with disordered memory. A task complexity effect would predict relative dating deficits to be greater in patients with more severe dementia, to be independent of disease group and to be more marked with more difficult memory tasks, but none of these predictions was fulfilled in this study. Further studies of PD patients have demonstrated disproportionate deficits in recency discrimination (Sagar *et al.*, 1985*b*, 1988) and in cognitive sequencing (Sullivan *et al.*, 1985). Although at present speculative, these observations, when taken together, suggest that impaired temporal judgement and poor sequencing may be associated processes that are specifically impaired in PD (Sagar, 1985, 1987). Such tasks are traditionally those associated with frontal-lobe function (Milner, 1971, 1974; Corsi, 1972; McFie and Thompson, 1972; Milner and Petrides, 1984). Impairment in temporal judgement and sequencing in PD are thus compatible with recognized abnormalities of frontal-lobe function in PD (Lees and Smith, 1983; Bès *et al.*, 1983; Wolfson *et al.*, 1985; Pillon *et al*, 1986; Taylor *et al.*, 1986; Sagar and Sullivan, 1988).

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# POSTURAL EFFECTS ON F WAVE PARAMETERS IN LUMBOSACRAL ROOT COMPRESSION AND CANAL STENOSIS

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## SUMMARY

The effects of standing, and lying with the back extended, on F wave minimal latency and F chronodispersion were studied in patients with lumbar canal stenosis, lumbosacral root compression syndromes, and low back pain. Standing for 3 min produced increased F chronodispersion in lumbar canal stenosis and root compression syndromes but had less effect on the F minimal latency. In patients with low back pain these variables were unchanged by these postural manoeuvres. These observations illustrate the value of adapting electrophysiological investigations to those clinical features that induce symptoms in these disorders.

## INTRODUCTION

Root pain and neurogenic claudication in patients with lumbosacral root disturbances, or lumbar canal stenosis, are often induced or aggravated by standing and walking (Dejerine, 1911; Blau and Logue, 1961; Hall *et al.*, 1985). Because nerve conduction studies after changes in limb posture are useful in the diagnosis of the posterior interosseous nerve entrapment syndrome (Rosén and Werner, 1980) and the carpal tunnel syndrome (Schwartz *et al.*, 1980) we have assessed the effect in patients with lumbar canal stenosis, root compression syndromes, and low back pain, using the parameters of F wave minimal latency and F chronodispersion (Kimura *et al.*, 1975; Eisen *et al*, 1977; Panayiotopoulos, 1979). F wave studies have been used in the diagnosis of lumbosacral root lesions, but not specifically in patients with lumbar canal stenosis (Fisher *et al.*, 1985).

## PATIENTS AND METHODS

### *Patients*

Thirty patients, aged 25 to 71 yrs (mean 50 yrs) were alloted on the basis of clinical, electromyographic and radiological features to one of three groups: (1) lumbar canal stenosis, (2) lumbosacral root compression and (3) low back pain.

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*Lumbar canal stenosis.* Ten patients (mean age 54 yrs) were studied. These patients presented with pain on walking or on standing, especially in the buttocks and posterior thighs. All but 1 patient had only mild limitation of mobility. There was clinical evidence of L5 or S1 root involvement in at least one limb, but conventional EMG studies detected bilateral root involvement in more than one limb in all patients. One patient had bilateral root involvement at the L3/4 level. In each patient the diagnosis was confirmed by CT scanning or myeloradiculography

*Lumbosacral root compression syndromes.* This group consisted of 11 patients (mean age 47 yrs) with unilateral lumbosacral root pain. EMG studies demonstrated neurogenic changes bilaterally in 3 patients, and unilaterally in 7; 1 patient showed no abnormality. In 7 patients root compression due to disc prolapse was shown in the CT scans or myeloradiculograms; in the remainder these investigations revealed abnormalities in root pouch filling without surgically amenable disc protrusion.

*Low back pain* In 10 patients (mean age 46 yrs) with nonradiating chronic low back pain, no objective clinical abnormality was detected. EMG studies were normal in all but 1 patient in whom long-standing neurogenic changes were detected in several leg muscles, but there was no evidence of active denervation. CT scans or myeloradiculograms were normal in the 6 patients investigated, including the patient with abnormal EMG studies

*Control subjects.* Ten healthy subjects aged 29–48 yrs (mean 40 yrs) were studied. None had clinical features of disease of the spine, cauda equina, or peripheral nervous system.

### *Electrophysiological methods*

All subjects were examined on a couch in a warm room. Both legs were studied in each subject. Individuals with cold limbs were warmed before investigation.

*Motor nerve conduction and concentric needle EMG studies.* Supramaximal stimuli were delivered to the peroneal and tibial nerves at the ankle. The evoked muscle action potentials (M responses) were recorded by surface electrodes placed over the extensor digitorum brevis muscle (L4/5) for peroneal nerve studies and the abductor hallucis (S1/2) for tibial nerve studies. Concentric needle EMG studies were carried out in all patients in quadriceps, gastrocnemius and tibialis anterior muscles, and in the appropriate paraspinal muscles.

*F response studies.* A supramaximal stimulus was applied at the same sites used for the motor nerve conduction studies. An amplifier gain of 100 $\mu$V/cm and oscilloscope sweep of 10 ms/cm were used. The filters were set between 20 Hz and 10 kHz. The F response latency was measured from the stimulus artefact to the first deflection of the evoked potential. A series of stimuli was used until 20 clearly demonstrable F responses were obtained (Kimura *et al.*, 1975). F wave persistence was not studied (Kimura *et al.*, 1984) In each nerve the shortest F response was plotted on a nomogram of data from normal subjects of various heights and minimal F response latencies within 2 SDs of the mean were accepted as normal. F chronodispersion was defined as the minimal/maximal F latency difference (Panayiotopoulos, 1979).

*Postural electrophysiological studies.* Each patient was asked to stand erect for 3 min. The electrophysiological procedures were repeated immediately, with the patient lying supine. Following a 3 min rest period, a pillow was placed under the small of the back producing hyperextension of the spine, in the lying posture, for 3 min. The electrophysiological studies were then repeated with the patient in this position. Identical studies were performed in control subjects.

*Data analysis.* Analyses of the F responses were based on the minimal latency and chronodispersion of these responses (Panayiotopoulos, 1979). The minimal F latency values obtained from the patients were compared with the normal values from the 10 control subjects. Absence of the F response, or a minimal F latency more than 3 SDs from the mean value in the control subjects was considered abnormal. The upper limit for F chronodispersion was 6.0 ms, i e., more than 3 SDs from the mean in the control subjects.

TABLE 1 F RESPONSE LATENCIES IN 10 CONTROL SUBJECTS*

| | *Rest* | | *3 min standing* | | *3 min lying* | |
|---|---|---|---|---|---|---|
| | *Tibial* | *Peroneal* | *Tibial* | *Peroneal* | *Tibial* | *Peroneal* |
| F minimal latency | 47.5+4.0 | 46.1+5.0 | 47.9+4.0 | 45.5+4.3 | 47.9+4.5 | 47.1+4.7 |
| F chronodispersion | 2.8+0.9 | 2.8+0.7 | 2.6+0.8 | 2.5+0.6 | 2.8+0.7 | 3.2+0.8 |

*All values in ms, means + 1 SD

## RESULTS

In all patients and control subjects motor and sensory nerve conduction velocities were normal in the peroneal, tibial and sural nerves.

### *Control subjects*

None of the control subjects developed any clinical symptoms during the postural tests. The mean values of the F response studies for the tibial and peroneal nerves are listed in Table 1. In the postural electrophysiological tests in the tibial and peroneal nerves the minimal F latency never increased more than 3.5 ms and F chronodispersion increased by more than 2 ms in only 1 nerve in which it increased by 4.5 ms. The mean values in these postural tests showed no change from the resting values.

### *Patients with lumbar canal stenosis*

None of these patients had symptoms when lying at rest, or with the lumbar spine extended but, in most patients, mild sciatic pain was induced by the standing test. The F response studies were abnormal in at least 1 of the nerves studied in all but 1 patient (Table 2). The F response was elicited in 39 of the 40 nerves studied. The minimal F wave latency was abnormal in 27 (69%) of 39 nerves in which the F response could be obtained. This yield of abnormality in F minimal latency measurements was not increased by the postural tests, although initially abnormal F wave minimal latencies tended to become more abnormal. Abnormal F responses at rest, after standing, or lying with the back arched were noted in 30 (77%) of the nerves. The major change in F wave latencies with postural tests was detected in the F chronodispersion measurements. In the initial resting studies 12 (31%) of 39 nerves showed abnormal responses. Six nerves in which F chronodispersion was normal at rest showed abnormal F chronodispersion in the standing test. In 3 of the patients there was a prominent increase in F chronodispersion in the standing test, but little change after lying with the back extended. In 1 patient, F chronodispersion in the left tibial nerve increased from 7.3 ms to 15.0 ms with standing, and to 8.7 ms when lying with the back extended. In a second patient, F chronodispersion in the left peroneal nerve was 7.0 ms at rest, 12.7 ms standing and 6.3 ms in the lying posture. In the third patient, F chronodispersion in the left peroneal nerve was 5.4 ms at rest, 11.8 ms standing, and 6.6 ms lying.

TABLE 2 LUMBAR CANAL STENOSIS AND LUMBOSACRAL ROOT COMPRESSION NUMBER OF NERVES SHOWING ABNORMAL F RESPONSE STUDIES

| | *Increased F minimal latency* | | *Increased F chronodispersion* | | *Abnormal in one or both tests* | |
|---|---|---|---|---|---|---|
| Lumbar canal stenosis (10 patients) | | | | | | |
| Rest | | | | | | |
| Tibial nerve (n = 20) | 15 | 75% | 5 | 25% | 14 | 70% |
| Peroneal nerve (n = 19)* | 12 | 63% | 7 | 37% | 14 | 74% |
| 3 min standing | | | | | | |
| Tibial nerve (n = 20) | 17 | 85% | 8 | 40% | 17 | 70% |
| Peroneal nerve (n = 19)* | 13 | 68% | 10 | 53% | 13 | 74% |
| 3 min lying | | | | | | |
| Tibial nerve (n = 20) | 17 | 85% | 5 | 25% | 17 | 70% |
| Peroneal nerve (n = 19)* | 13 | 68% | 8 | 42% | 13 | 74% |
| Lumbosacral root compression (11 patients) | | | | | | |
| Rest | | | | | | |
| Tibial nerve (n = 21)* | 6 | 28% | 1 | 5% | 7 | 33% |
| Peroneal nerve (n = 21)* | 3 | 14% | 0 | 0% | 3 | 14% |
| 3 min standing | | | | | | |
| Tibial nerve (n = 21)* | 8 | 38% | 3 | 14% | 10 | 48% |
| Peroneal nerve (n = 21)* | 4 | 19% | 3 | 14% | 7 | 33% |
| 3 min lying | | | | | | |
| Tibial nerve (n = 21)* | 8 | 38% | 1 | 5% | 8 | 38% |
| Peroneal nerve (n = 21)* | 5 | 24% | 0 | 0% | 5 | 24% |

*No F response elicited in one of the nerves

## *Lumbosacral root compression syndromes*

Most patients in this group did not develop symptoms during the postural tests, but 2 patients had mild sciatic pain while standing. At rest, 7 of 11 patients showed abnormal F responses in 10 (24%) of the 42 nerves in which F responses could be obtained (Table 1). Nine nerves had increased minimal F latencies and 1 had increased F chronodispersion with a normal minimal F wave latency. In the standing test, 8 patients developed abnormal minimal F latencies and/or increased F chronodispersion in one or more nerves. These changes occurred in 17 (40%) of the 42 nerves studied (Table 2). In 1 patient the abnormal F chronodispersion elicited in the standing test was the only abnormality. Thirteen (31%) of the nerves studied were found abnormal in 7 patients when lying with the back arched. In 8 nerves, F chronodispersion increased in the stress tests. In 2 patients there was a prominent increase in F chronodispersion with standing. One showed left peroneal F chronodispersion 2.7 ms at rest, 2.8 ms standing, and 3.2 ms lying with the back extended. In the second patient left F peroneal chronodispersion was 3.8 ms at rest, 10.8 ms standing and 2.4 ms lying. The minimal F latency became abnormal in 4 nerves following the standing or lying postural tests.

## *Patients with low back pain*

In 9 of the 10 patients in this group, F response studies were normal at rest and in the postural tests. In 1 patient the left peroneal F chronodispersion was normal at rest (3.5 ms) increased with the standing test (7.0 ms) and was normal in the lying test (2.0 ms).

### *F responses and clinical lateralization*

In the patients with lumbosacral canal stenosis, the F response studies showed bilateral involvement in 6 of the 9 patients, both at rest and with postural tests. One patient, who had bilateral pain, had normal F response studies. In the patients with lumbosacral root compression syndromes, the F response studies at rest showed unilateral abnormalities in 5 patients and bilateral abnormalities in 2. In the standing tests, 7 patients in this group developed bilateral F wave abnormalities and 1 had unilateral abnormalities. All these patients had unilateral root syndromes. Only 1 patient with low back pain showed abnormalities, and only 1 nerve in this patient was abnormal.

## DISCUSSION

This investigation shows that the clinical effects of postural change in patients with lumbosacral canal stenosis and root compression syndromes can be correlated with changes in proximal motor conduction, when these postural effects are replicated in standardized tests in the electrophysiological laboratory. The principal change occurred in F chronodispersion. The yield of abnormality using this measurement increased from 31% at rest to 47% with postural tests in patients with lumbar canal stenosis and from 2% to 14% in patients with lumbosacral root compression syndromes. In the group with canal stenosis, the overall yield of abnormality in F wave responses increased only slightly from 69% at rest to 77% with postural tests, but it increased from 23% to 41% in the group with root compression syndromes. F wave studies with postural tests were also helpful in demonstrating bilateral or multiple root involvement in both these groups of patients, even in the presence of clinically unilateral disease.

The F response latency has been reported abnormal in 18 to 65% of patients with lumbosacral root disturbances (Fisher *et al.*, 1978; Eisen *et al.*, 1977; Tanzola *et al.*, 1981; Aminoff *et al.*, 1985). The patients described in these studies (Kimura *et al.*, 1975, 1984; Magnaes, 1982*a*; Hall *et al.*, 1985) were all investigated at rest, using routine electrophysiological methods. In our patients, the F minimal latency was increased or absent in 1 or more nerves in 21% of patients with lumbosacral root compression syndromes, a result comparable to previous reports. In lumbar canal stenosis, the F minimal latency at rest was increased in 69% of nerves studied. In previous reports, patients with canal stenosis have not been investigated with F wave studies.

F chronodispersion, a measure of the variability of conduction in different motor axons in a nerve (Panayiotopoulos, 1979), increased the yield of abnormality both in patients with lumbar canal stenosis and lumbosacral root compression (Table 2). In the 21 patients in these two groups, only 4 nerves, normal at rest, became abnormal in terms of minimal latency following the standing or lying test. In contrast, F chronodispersion became abnormal in 11 nerves following standing. This suggests that some fibres developed conduction abnormality during these tests.

Clinical manoeuvres such as the stoop test (Dyck, 1979), range of spinal motion, and the straight leg raising test, have been devised to evaluate posture dependent symptoms (Dyck, 1979; Pope *et al.*, 1979). The effect of postural change on the spinal canal and the dural sac can be demonstrated at myelography (Penning and Wilmink, 1981). A nerve root may be compressed by a change in posture from several mechanisms. These include vertebral subluxation induced by the upright posture, posterior encroachment upon the spinal canal by the ligamentum flavum in lumbar extension, and anterior encroachment upon the lumbar canal by herniated disc (Penning and Wilmink, 1981; Magnaes, 1982*a*, *b*). A prominent increase in intraspinal pressure with changes in posture may be an important factor in symptom production in patients with lumbar canal stenosis (Magnaes, 1982*b*) since this may itself impair venous return in the caudal spinal canal. Standing and walking can produce an increase in intraspinal pressure which may exceed the mean arterial blood pressure in patients with lumbar canal stenosis (Magnaes, 1982*a, b*) and motor and sensory conduction velocity may be slowed in the cauda equina in these patients (Tsuji *et al.*, 1985; Swash and Snooks, 1986). In our patients with low back pain without other clinical features, the resting F wave studies showed no abnormality, and there was no change with postural tests.

In the electrophysiological investigation of lumbosacral canal and root disorders, concentric needle EMG is usually the single most useful diagnostic test (Aminoff *et al.*, 1985) because it is informative in demonstrating denervation in the recognition of root lesions. F wave studies provide complementary information and may sometimes reveal abnormalities when the EMG data are unhelpful (Schwartz *et al.*, 1980; Tanzola *et al.*, 1981). F wave studies in the tibial and peroneal nerve in each leg, as in our study, should be especially useful in identifying lumbar canal stenosis since the electrophysiological evidence of multiple and bilateral root involvement revealed by these investigations suggests canal stenosis rather than isolated root compression syndromes. In contrast to conventional needle EMG investigations, F chronodispersion studies (Panyiotopoulos, 1979) seem particularly sensitive to the dynamic effects of postural change. The addition of postural tests to resting F wave latency measurements increases the specificity of the electrophysiological investigation in relation to the particular clinical features, since postural effects are well-known and important aspects of these syndromes.

## ACKNOWLEDGEMENT

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# BOOK REVIEWS

**Epilepsy in Young People.** Edited by Euan Ross, David Chadwick and Robert Crawford. 1987. Pp. 169. Chichester: John Wiley. Price £21.95.

This small book results from a symposium held in Portsmouth in June 1986, sponsored by Ciba-Geigy. The company did well to bring together most of those in the United Kingdom interested in epilepsy in childhood and adult life. All too often there is insufficient contact between paediatric and adult neurologists and, writing as one of the latter, it was certainly useful to hear the contributions of my paediatric colleagues. The book itself reflects the good nature of the meeting. Particularly interesting is a chapter by Kurtz and colleagues updating the information available on the incidence and prevalence of epilepsy in childhood, based upon the National Child Development Study, following more than 17,000 children born in one week in 1958. In an episodic illness such as epilepsy, which starts and stops, my own view is that it is helpful to have information about the cumulative incidence, and perhaps in any future publication the authors can display graphically what is apparent only with difficulty from their complex tables. Nonetheless, this study is a model of what epidemiology should be all about.

Ian McKinlay underlines the problem that afflicts both paediatric and adult neurologists—the difficult period of transition in adolescence. All too often, a child with intractable epilepsy is reasonably well accommodated within the educational system but, as soon as he becomes too old for school, his social isolation increases and the quality of his experience of life declines.

Other chapters provide useful summaries of anticonvulsant treatment in young people, and there is a good but brief summary by Pamela Crawford of anticonvulsant drugs under current development. Of those mentioned, progabide already looks likely to fall by the wayside, but enthusiasm continues to grow for gamma vinyl GABA, in spite of continuing concern about the unusual intramyelinic oedema apparent in some experimental animals. There is also a useful review by Arnold Wilkins on photosensitive epilepsy and visual display units, particularly relevant to young people with epilepsy entering employment.

This is a satisfactory little book that was a pleasure to read.

ANTHONY HOPKINS

**Electrical Stimulation and Neuromuscular Disorders.** Edited by W A Nix and G. Vrbova. 1986 Pp. 147. Berlin: Springer Price DM 98.00.

This slim volume comprises the Proceedings of the First International Symposium on Electrical Stimulation and Neuromuscular Disease held in Mainz, West Germany, March 29–30, 1985. The fourteen chapters are grouped into three sections (1) The effects of nerves on muscles—including reports of the role of activity in the development of the mammalian motor unit, the adaptive response to chronic stimulation and effects on capillary supply. Further pages in this section cover the neural control of the acetylcholine receptor and factors influencing motor nerve growth. (2) Repair processes in the peripheral nervous system, neural activity and the reorganization of motor units in reinnervated skeletal muscle, electrical activity in injured peripheral nerves and assessment of the regenerative capacity of peripheral (somatic and autonomic) nerves. (3) Muscle plasticity in disease This section still largely covers experimental models in animals, but the volume concludes with two clinical studies of the effects of electrical stimulation on normal and diseased human muscle and the treatment of idiopathic scoliosis with daily short-term electrostimulation.

The volume includes a valuable review of the studies of several of the most distinguished workers in the field. As a review of possible experimental models for physiological or pathological study, it is far more impressive than as a guide to future clinical applications. Those described are specifically selected and not without their practical problems or criticisms. So far the results do not indicate that widespread clinical application is either desirable or practical. This does not mean, however, that further research is not indicated of the effects of chronic electrical stimulation on muscle structure and function in selected clinical conditions.

This book is likely to be of more interest to scientists interested in possible clinical applications than to clinicians interested in applying chronic electrical stimulation in the treatment of neuromuscular disorders. For the clinician there is also the related field of 'functional electrical stimulation' of particular interest for the management of paraplegia but this is not covered in this volume. The price seems high for such a slim volume but this is not uncommon with such publications.

R H T. EDWARDS

**Modern Neurosurgical Giants.** Edited by P. C. Bucy. 1986. Pp. 497. New York: Elsevier. Price: $69.25.

In this volume, a sequel to *Neurosurgical Giants Feet of Clay and Iron* published in 1985, its distinguished editor has collected about 80 articles on neurosurgeons prominent in the last 50 years, most of them still living. That is, perhaps, the weakness of the book, which is certainly less appealing than the previous one. A haze of hagiography hangs heavily about most of them making it often difficult to discern the outlines of the subject or to read the matter without disbelief.

The first volume contained many frank accounts of older surgeons who are safely dead, including Bailey's remarkable article on Cushing; into this, one criticism rarely enters though it provides a welcome relief when it does, as in Bucy's comments on why he could not stand Loyal Davies, or the remark that many of Schwartz's trainees contemplated leaving at one time or another because of the abuse to which they were subjected.

Yet there is much of interest in the book if it is sought out, for most of the great names in neurosurgery from the thirties onwards are here and the biographical information provided must be of value to any neurosurgeon with a proper interest in the growth of his specialty. Americans naturally predominate but there is a reasonable representation of British, Continental, Spanish-American and Japanese, two Russians and even an Australian. The authors are mainly protégés of their subjects and, as in the *Dictionary of National Biography*, authorship of an article seems to increase the chances of being the subject of a subsequent one. The pieces might, perhaps, have been of more interest and less liable to finish up as an exercise in panegyric, if someone more remote had been chosen to pen them. The most successful are those in which the writer has chosen to be factual about the work and life of the surgeon, though this is carried too far in the case of Arseni where the unfortunate subject has finished up with little more than a list of his appointments and publications. The lineage of many distinguished figures is traced so that one can see who trained with whom and where and how the world of neurosurgery has been colonized. A little humour, perhaps unconscious, enters at times as when we are told how a distinguished professor of neurosurgery on the west coast of America, disabled with a broken leg, sustained a temporary brachial plexus palsy through operating on a head injury while supported on crutches under his gown.

Perhaps the most remarkable feature of these two volumes is the contribution of the Editor, now in his eighties, who has known most of the biographical subjects, whose own career spans more than 50 years and who contributes, to most of the articles, an afternote. Though some of these are bland, many throw a brilliant shaft of critical light on the personality just outlined.

This volume, with its companion, would serve a useful purpose in any departmental library by providing neurosurgeons, especially those in training, with a selected biographical dictionary of their subject.

T. T. KING

**The Cognitive Neuropsychology of Language.** Edited by M. Coltheart, G. Sartoni and R. Job. 1987. Pp. 418. London: Lawrence Erlbaum. Price £29.95.

The editors of a volume of conference papers, particularly when the topic is a relatively new field of study, often find themselves in a dilemma. Are they to impose a structure on the papers, however strained, grouping them into themes and introducing each section with a rehearsal of the issues? Or are they to let the heterogeneity of the new field display itself and leave the reader to make inferences? The editors of this book have largely taken the second option. One of them (Coltheart), however, has provided an introductory chapter, which picks out prominent themes in the unordered papers, while a different contributor, Ellis, provides an end chapter which draws from these conference papers the general message that the days of aphasia 'syndromes' are over and the dawn of the new era of 'symptom profiling' is already spreading its glow.

The uniting theme of the book is the application of the notions of modules to the mental processing of language. A system which operates in modules has the advantage that one part can be impaired without necessarily affecting others, and that processing can operate in parallel if it does not engage identical modules. Much of current work in cognitive neuropsychology is directed at showing how the behaviour of brain-damaged individuals justifies such a fractionation of mental processing. Coltheart's introduction summarizes one current model of how single words (and nonwords) may be processed in transcoding from listening and reading to speech and writing. He shows how some of the following chapters are not only relevant to endorsement of aspects of this model but also how they suggest further refinements of it. He also anticipates Ellis' paper in pointing out that others of the papers which deal with the processing of sentences lead logically not only to the abandonment of Broca's aphasia as a syndrome, but also to the abandonment of the notion of 'agrammatism'.

As might be expected from this first collection of papers in book form on the cognitive neuropsychology of language, the majority of the papers are single case studies. It is only necessary for one patient to show a distinctive fractionation of language for a revision of the model to be proposed for further testing. Howard's paper describes a patient conventionally categorized as a severe Broca's aphasic, who was unable to match upper and lower case letters, although he was nevertheless able to read aloud correctly about a third of the sets of words presented to him, regardless of which case they were presented in (printing or handwriting). If their visual configuration was altered, however, by separating the letters by plus signs or writing them diagonally, his performance was much worse. From this Howard infers that reading does not necessarily depend on a preliminary identification of letters (as the basic model discussed by Coltheart proposes), but that word-shape information can provide alternative access to the visual input lexicon.

In Howard's paper an expansion of a section of the model is being proposed. In some of the other papers, other parts of the model are being used to make hypotheses as to the locus of the principal malfunction in the individual patient, deducing from this what other behaviours should necessarily follow and confirming that they do. Chapter 4, for example, by Bub and colleagues, locates to the Phonological Response Buffer the reading difficulties of the 67-year-old housewife they investigated, and predicts (correctly) that she would consequently have difficulty in repetition of heard speech. Other papers which use a similar approach are those co-authored by the two Italian editors of the book, as well as those by Miceli and colleagues, by Patterson and Shewell and by Kremin. Each describe individuals with reading and spelling disorders. With the Italian editors' paper we come across a slight difficulty. They apply, not the model expounded by their fellow editor, but a somewhat different logogen model. They claim that their case provides evidence that grammatical class and concreteness are not represented in the 'cognitive system' but must be in the 'visual input logogen system'. It is not clear whether this input logogen system is considered to be identical to the orthographic input lexicon in the Coltheart model, in which case a principal modification to the nature of this module is being suggested, or whether a more radical fractionation of the language system into different modules is being advocated. It seems a pity that such a confusion arises from chapters constructed by the editors themselves, given the need for an agreed terminology in this complex area.

Patterson and Shewell's model is the basis for the one described in Coltheart's introduction, and interpretation of their claim that their 76-year-old ex-hospital clerk's aphasia shows that spelling is possible without the use of phonology is easier. Kremin's case, a 34-year-old graduate teacher, provides further evidence for this, and for an additional claim that writing can be achieved by a lexical but nonsemantic route, since he was equally effective at writing words which he understood or did not understand. Denes and colleagues' chapter (one of two concerned with developmental disorders) provides further evidence of the independence of spelling from phonology. It describes an 11-year-old boy with Landau-Kleffner syndrome who was word-deaf and produced very few words, but whose written language was nevertheless almost normal.

Like Sartori and colleagues, Miller and Ellis have related their case study to a logogen model, though their main thrust is to incorporate into it the notion of partial activation of words consistent with an interactive activation model. Neologistic jargon aphasics like their patient seem to have a difficulty in activating lexical units in the phonological and orthographic output lexicons. This patient's attempts at self-correction on a naming task resulted in worse rather than better productions, suggesting that each attempt at a word was a new effort at activating the lexical item rather than a modification of the previously produced one.

Another kind of disturbance, disturbance of lexical semantics, is reviewed by Shallice, who sets out the case not only for multiple semantic representations (i.e., visual, auditory, tactile and verbal) but for subdivisions within these systems specific to sensory properties and functional significance. Keeping the classical distinction in semantic disorders between impairment in a store and in access to a store (a distinction which is being increasingly questioned by proponents of representation through activation and of connectionism), Shallice suggests five criteria by which disorders of 'degraded store' can be distinguished from disorders of access, i.e., consistency, reaction to priming, invariance of order of loss of attribute information, frequency of the item and the influence of varying the rate of presentation. He shows how the small group of patients he studied appeared to be differentiated into two types by these criteria.

Despite Ellis's strictures against syndromes, Seymour preserves the syndrome terminology of phonological dyslexia, morphemic (surface) dyslexia and visual analytic dyslexia in his information-processing analysis of developmental disorders of reading, the other chapter which considers children's disorders.

Five chapters in the book consider aphasia beyond the single word level. The chapters by Schwartz, Berndt and Parisi, respectively, deal with sentence production. Parisi demonstrates that the problems of sentence construction labelled as agrammatism in 8 patients and as paragrammatism in 2 patients in fact formed a continuum when analyses of sentence length and of errors in grammatical morphemes (affixes and free function words) were made. Parisi considers that grammatical morphemes are drawn from a separate lexicon from the one containing the knowledge store of content words. Berndt's analysis of 6 patients' speech offers a complementary interpretation. Studying in particular patients identified as agrammatic, she distinguishes two problems, those related to sentence construction and those related to insertion of grammatical morphemes. Schwartz's chapter provides an alternative account of this morphological/constructional division. Applying Garrett's model of sentence production (essentially derived from analysis of speech errors in normal subjects) and LaPointe's modifications, she suggests that the morphological deficit may be related to defective sound sequencing procedures restricting the phonetic production of grammatical morphemes, while a difficulty in utilizing the morphosyntactic fragments from which sentence planning frames are built leads to a constructional disorder. Schwartz acknowledges that this account offers no explanation of those morphological disorders which occur without either articulatory or constructional difficulties. In applying Garrett's model to Wernicke's aphasia, Schwartz locates the disorder in the inventories which represent the meanings and grammatical category of words, as well as their segmental (phonological) form.

The two papers which describe sentence comprehension disorders use different strategies for investigation. Tyler uses reaction times to probes as the patient is listening to types of sentences which vary in their violations of syntax, semantics and pragmatics, in order to tap real-time sentence processing. She shows that this technique can provide more information than error counts. For example a young agrammatic man was shown to rely on pragmatic appropriateness; his syntactic deficit in comprehension was identified as an inability to construct whole sentence representations rather than local constituents. Caplan's technique is to ask patients to manipulate toy animals or dolls to show how they have understood sentences varied on linguistic parameters. The sentences used here were all pragmatically unusual, e.g., The frog hit the elephant that kissed the rabbit. The author's interest in more formal grammars is evident, and later publications of Caplan and his colleagues in the journals Cognition and Cognitive Neuropsychology show how this technique is being used as a medium for applying Chomskian government and bind theory as an explanation for the difficulties aphasic patients have in comprehending sentences.

What all these papers have in common is not only their interpretation of aphasic disorders from a rich basis of theory, but the attention they pay to rigorous collection of data, exploration of alternative interpretations and corroboration through statistical tests. Inevitably some of the findings conform to clinical intuition, and others do not; but within the restrictions imposed by the perspective of cognitive neuropsychology (e.g., its focus on mental processing in language rather than the sociolinguistic functions of communication) the approach brings a logic and power of explanation which the field of aphasiology has hitherto lacked. The book gives a good sample of what this new approach can offer. From the above summaries, however, it will be clear that the reader of this book is left to make his or her own synthesis of the disparate work which is being done in this field. In this repect the book is not dissimilar to a bound volume of the current journal which is devoted largely to this theme. Nevertheless, if the reader has the patience to make the synthesis, there is a rich exposition here of the fertility of this new approach to analysing aphasia.

RUTH LESSER

**Brain Systems, Disorders and Psychotropic Drugs.** By Heather Ashton. 1987. Pp. 547 Oxford University Press Price £40 00.

In this era of edited books, it is a pleasure to review one which comes from a single author, who attempts the difficult topic of uniting knowledge from the fields of pharmacology, neurochemistry and neuroanatomy with clinical data. The book is divided into five parts, covering arousal and sleep, reward and punishment, learning and memory, depression and mania, and schizophrenia. In general, the underlying anatomy and neurochemistry is presented before description of the clinical disorders, which is followed by a chapter on drugs that act on the subject under discussion. For example, in the section on arousal and sleep, the limbic system and the underlying anatomy of arousal and attention are presented before discussion of neurochemical involvements in sleep, and the electrophysiological measurement of sleep. Disorders of arousal and sleep are then described, including anxiety and sleep disorders, followed by a chapter on hypnotics, sedatives and anxiolytics which discusses the pharmacokinetics and pharmacodynamics of the various chemical compounds.

The chapters are extremely comprehensive, well referenced, and provide an excellent overview for those interested in exploring the topics reviewed in some detail. This is not a book for the beginner or the browser, but one for a serious student of the brain sciences who wishes to have not only a useful reference book of up-to-date research, but who has sympathy for the concept that the basic sciences and clinical practice need uniting as closely as possible. It will be of value to neurologists who are interested in the brain and behaviour, and for neuroscientists who want an up-to-date overview of some specific areas of biological psychiatry.

MICHAEL R. TRIMBLE

# ANNOUNCEMENTS

### 23rd Canadian Congress of Neurological Sciences

This will be held at the Chateau Frontenac, Quebec City, Canada, on June 14–18, 1988 For information, contact Dr Gerard Le Blanc, Department of Neurosciences, Infant Jesus Hospital, 1401 18th Street, Quebec City, PQ, Canada G1J 1Z4 (Tel 418-694-5756).

### Fyssen Foundation 1988 International Prize

The general aim of the Fyssen Foundation is to encourage all forms of scientific enquiry into cognitive mechanisms, including thought and reasoning, underlying animal and human behaviour, into their biological and cultural bases and into their phylogenetic and ontogenic development For this purpose a substantial *International Scientific Prize* will be awarded for a major contribution to the progress of knowledge in the fields of research supported by the Foundation such as ethology, palaeontology, archaeology, anthropology, psychology, epistemology, logic and the neurosciences. The discipline for the 1988 Prize is Epistemology—Logic of Knowledge

Nominations for the 1988 Prize should be sent (15 copies) to the Secretariat of the Foundation, 194 rue de Rivoli, 75001 Paris and should include a curriculum vitae of the nominee, a list of his publications and a summary (4 pages maximum) of the research upon which the nomination is based

Nominations must be received by September 1, 1988.

### International Congress on Neurovascular Disease

This will be held at The Sheraton Hotel, Innsbruck, Austria, on May 26–28, 1988 For further information, contact S. Weimann, Department of Vascular Surgery, Anichstrasse 55, A6020 Innsbruck, Austria (Tel 0 55 22/723/25 70)

### New York Academy of Sciences

A conference on *Arachidonic Acid Metabolism in the Nervous System Physiological and Pathological Significance* will be held in the Hyatt Regency Hotel, Bethesda, Maryland, USA on April 14–16, 1988. For further information, contact Conference Department, New York Academy of Sciences, 2 East 63rd Street, New York, NY 10021 (Tel (212) 838–0230).

### European Neurological Society

The European Neurological Society (ENS) has been founded to foster cooperation between neurologists and those working in related disciplines within Europe. Meetings will be held biennially. The participation of individuals from other areas of the world is welcomed. The biennial meetings will provide instructional courses for neurologists in training, up-date symposia, and sessions for the presentation of original work, either as platform or poster presentations. The first meeting will be held in Nice from June 19–21, 1988, when the teaching programme will include courses on peripheral neuropathy, neuroimaging, ageing and dementia, and neurovirology/neuroimmunology There will be symposia on physiological and pathological aspects of cerebral blood flow, clinical neuropharmacology and neurogenetics.

Active membership of the ENS will be by election from clinicians and scientists whose chief interest is directed towards practice, teaching or research in neurology and cognate fields. Active membership will become effective only after contribution to a meeting of the ENS Junior members may be elected from members engaged in postgraduate studies in neurology or related disciplines

Further information about the ENS, together with registration and abstract forms for the first meeting, may be obtained from the Secretary, Professor G Said, Service de Neurologie, Hôpital de Bicêtre, 94287 Le Kremlin Bicêtre Cedex, France Abstract forms must be returned by February 1, 1988.

### Association of the Czechoslovak Medical Societies J. E. Purkyně and the Czechoslovak Society of Neurology

These Societies will be organizing the *1st European Congress of Neurology* in Prague, Czechoslovakia, on April 18–22, 1988 under the auspices of the World Federation of Neurology. Further information may be obtained from Dr J. Dolanský, Secretary General, Vitezneho unora 31, 120 26 Praha 2, Czechoslovakia.

### Symposium on Art and the Brain

This symposium, sponsored by the Neurology Department of the Michael Reese Hospital, Chicago, the Art Institute of Chicago with assistance from the Brain Education Center of California State University, will be held n May 12–14, 1988 at the Art Institute of Chicago Further information from Andrea Gellin Shindler, Department f Neurology, Michael Reese Hospital, Lake Shore Drive at 31 Street, Chicago, IL 60616 (Tel. (312) 791–4481).

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**The neuropathology of the acquired immune deficiency syndrome (AIDS): a review.** F. Gray, R. Gherardi and F. Scaravilli 245

**Orienting of visual attention in progressive supranuclear palsy.** R. D. Rafal, M. I. Posner, J. H. Friedman, A. W. Inhoff and E. Bernstein 267

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**Internal versus external cues and the control of attention in Parkinson's Disease.** R. G. Brown and C. D. Marsden 323

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**Changes in presynaptic inhibition of Ia fibres in man while standing.** R. Katz, S. Meunier and E. Pierrot-Deseilligny 417

**Kinematic analysis of multiple movement coordination during speech in stutterers.** A. J. Caruso, J. H. Abbs and V. L. Gracco 439

**Pure word deafness (acquired verbal auditory agnosia in an Arabic speaking patient.** B. A. Yaqub, G. G. Gascon, M. Al-Nosha and H. Whitaker 457

**Book reviews** 467

**Announcements** 478

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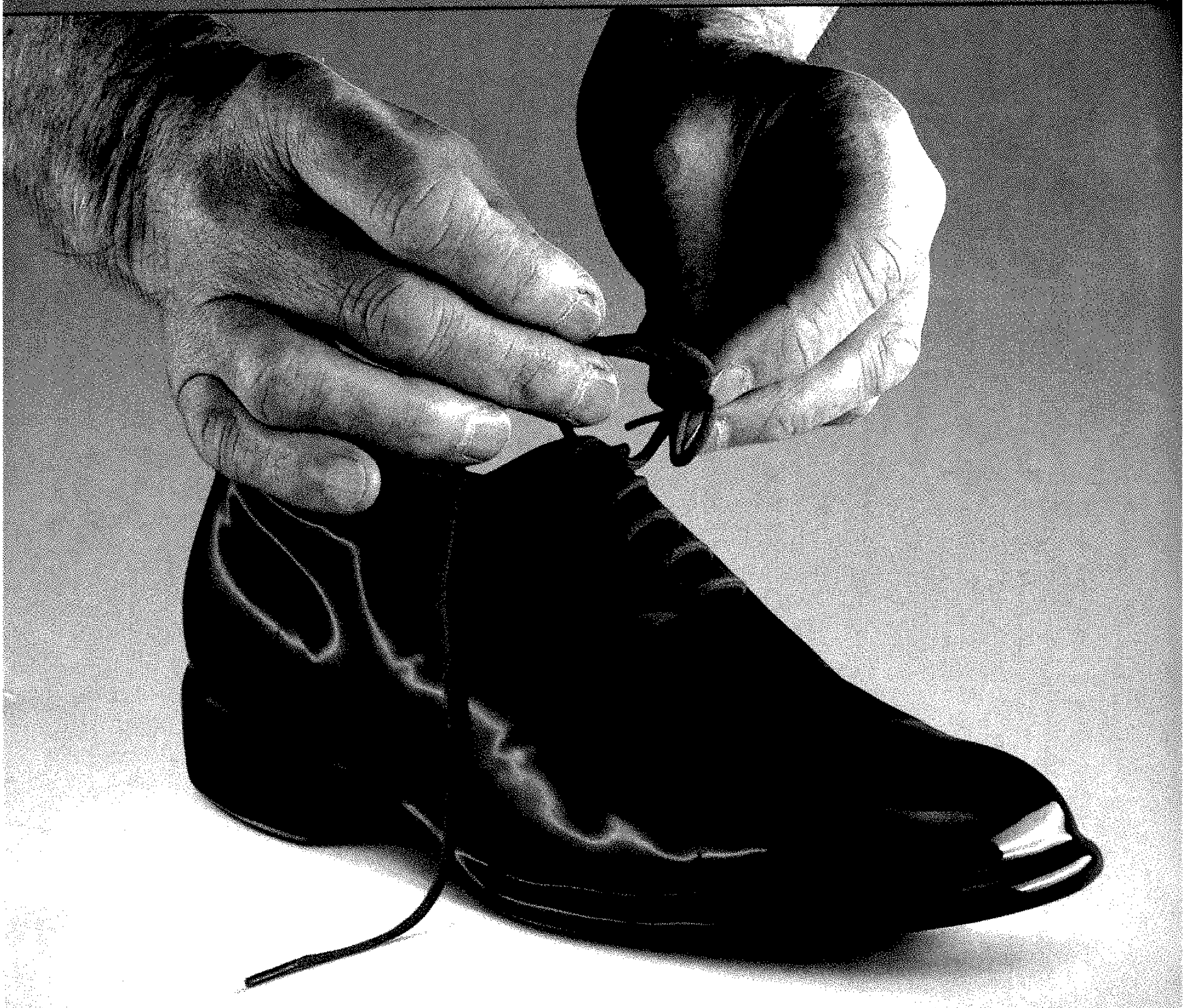

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# THE COEXISTENCE OF BRADYKINESIA AND CHOREA IN HUNTINGTON'S DISEASE AND ITS IMPLICATIONS FOR THEORIES OF BASAL GANGLIA CONTROL OF MOVEMENT

*by* P.D. THOMPSON, A. BERARDELLI, J.C. ROTHWELL, B.L. DAY, J.P.R. DICK, R. BENECKE *and* C.D. MARSDEN

(*From the MRC Movement Disorder Research Group, University Department of Neurology, and the Parkinson's Disease Society Research Centre, Institute of Psychiatry, and King's College Hospital Medical School, London*)

## SUMMARY

Investigation of motor function in a group of 17 patients with Huntington's disease reveals that, in addition to the chorea that many patients exhibit, defects in voluntary motor performance also are evident. Fast simple wrist flexion movements to 15° or 60° were slower, and individual movements showed greater variability than seen in normal subjects. This bradykinesia was most pronounced in those patients who were akinetic and rigid, but also was seen in those with chorea alone, bradykinesia was independent of the drug treatment that the patients were receiving (and was therefore not due to drug-induced parkinsonism). The electromyographic activity of the agonist muscles during such simple but slow movement differed from that seen in Parkinson's disease. The performance of complex movements revealed further deficits Some patients were unable to combine two movements in a simultaneous or sequential movement task of squeezing the hand and flexing the elbow. Those who could perform these complex movements exhibited slowing of the velocity of the movement and prolongation of the interval between movements. These abnormalities were present in patients with chorea who were not taking neuroleptic drugs. It is argued that they represent an abnormality of motor programming of complex movements, over and above the defect in executing simple movements. The long latency stretch reflexes in wrist flexor muscles and flexor pollicis longus were reduced or absent, but this did not correlate with changes in motor performance, or with the reduced size of the early components of cortical sensory evoked potentials. Bradykinesia is thus shown to be an integral component of the motor disorder of Huntington's disease, in addition to the chorea. The coexistence of bradykinesia and chorea in this illness is compatible with current theories of the role of the basal ganglia in the control of movement

## INTRODUCTION

Although the most conspicuous abnormality of movement in Huntington's disease is chorea, involuntary movements may not be the sole, or even the major source of motor disability in this condition. Several authors have drawn attention to the

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fact that pharmacological suppression of chorea may not lead to improvement of motor function (Shoulson, 1981; Girotti *et al.*, 1984; Quinn and Marsden, 1984; Koller and Trimble, 1985). An underlying deficit reminiscent of the akinesia/bradykinesia of Parkinson's disease remains or even deteriorates with treatment of the chorea. Indeed, some patients with Huntington's disease may present with an akinetic-rigid syndrome (the'Westphal' variant) without typical chorea, and it is well known that with the passage of time and progression of the disease, chorea may subside and an akinetic-rigid and often dystonic syndrome emerges (Hamilton, 1907–8; Denny-Brown, 1960; Bittenbender and Quadfasel, 1962; Hayden, 1981).

These clinical observations hint at the concept that akinesia/bradykinesia may be a fundamental motor abnormality in Huntington's disease in addition to the characteristic chorea. Such a conclusion would be in keeping with contemporary concepts of the motor functions of the basal ganglia, which conceive of these structures as necessary for the initiation and execution of movements. However, there have been relatively few studies into the motor pathophysiology of Huntington's disease.

Studies of gait (Koller and Trimble, 1985) have disclosed abnormalities resembling those in Parkinson's disease; patients had difficulties initiating gait and in turning, and there was an increased step cycle time and slow leg swing. Hefter *et al.* (1987) have reported slowing of finger movements. Moreover, there may be striking slowing of voluntary saccadic eye movements in some patients with Huntington's disease (Starr, 1967; Leigh *et al.*, 1983) in contrast to the limb chorea.

Despite clinically normal sensory function, cortical somatosensory evoked potentials (SEPs) to peripheral nerve stimulation may be small or absent (Noth *et al.*, 1984, Bollen *et al.*, 1985), while long-latency stretch reflexes are often absent (Noth *et al.*, 1985). In contrast to these afferent abnormalities, the corticomotoneuron connections as tested by electrical stimulation of the motor cortex, conduct normally (Thompson *et al.*, 1986). The relationship of the disturbances of the central processing of afferent information to the disorder of movement remains unclear.

In the present paper we have examined the voluntary control of simple movements and complex simultaneous and sequential movements of the arm and hand in patients with Huntington's disease of varying severity. The clinical signs, voluntary movements, SEPs and stretch reflexes in individual patients were assessed to see if any correlation existed between them. The results will be discussed in the light of the known pathophysiological changes that occur in Parkinson's disease, a disorder of the basal ganglia which presents a clinical syndrome of akinesia/bradykinesia, in contrast to the hyperkinesia of Huntington's disease. Part of this work has been published in abstract form (Berardelli *et al.*, 1985; Thompson *et al.*, 1985).

## PATIENTS AND METHODS

### *Patients*

The clinical features of the 17 patients with Huntington's disease in this study are summarized in Table 1. They comprised 9 males and 8 females aged between 36 and 67 yrs (mean age 48 yrs) with a disease duration of between 4 and 20 yrs (mean 10 yrs). The diagnosis of Huntington's disease was established on the basis of the clinical features and a family history of the disease in all cases The patients have been ranked in the table on clinical grounds, according to the severity of their chorea.

TABLE 1 SUMMARY OF CLINICAL FEATURES, DRUG THERAPY, LONG-LATENCY STRETCH REFLEXES (SR) AND CORTICAL SENSORY EVOKED POTENTIALS (SEPs) IN 17 PATIENTS WITH HUNTINGTON'S DISEASE

| | | | | | | *SR* | | |
|---|---|---|---|---|---|---|---|---|
| | *Case* | *Age (yrs)* | *Sex* | *Disease duration (yrs)* | *Drugs* | *FF* | *FPL* | *SEP* |
| Akinetic-rigid | 1 | 64 | F | 20 | Pimozide | + | NP | + |
| | 2 | 54 | F | 10 | Tetrabenazine, pimozide, thiopropazate | + | + | − |
| | 3 | 59 | M | 15 | Pimozide | + | + | + |
| | 4 | 39 | F | 7 | — | + | + | + |
| Mild to moderate chorea | 5 | 44 | M | 6 | Baclofen | + | + | + |
| | 6 | 39 | M | 8 | — | + | − | + |
| | 7 | 60 | M | 15 | Baclofen | + | − | + |
| | 8 | 52 | M | 10 | Sulpiride | + | + | NE |
| | 9 | 36 | F | 4 | — | + | − | + |
| | 10 | 67 | M | 10 | Baclofen | + | − | − |
| Severe chorea | 11 | 37 | M | 9 | Tetrabenazine, pimozide | + | − | + |
| | 12 | 52 | F | 15 | Pimozide | + | + | + |
| | 13 | 40 | F | 5 | Pimozide | − | − | − |
| | 14 | 46 | F | 14 | Tetrabenazine, pimozide | − | − | − |
| | 15 | 58 | F | 15 | Tetrabenazine, tiapride | + | − | − |
| | 16 | 40 | M | 10 | Tetrabenazine | + | − | − |
| | 17 | 36 | M | 5 | Tetrabenazine | + | NP | − |

FF = forearm flexors, FPL = flexor pollicis longus + = present, − = absent, NP = not possible, NE = not examined

Four patients were akinetic (Cases 1–4), 1 (Case 1) profoundly so, to the extent that she was capable of very little voluntary movement, and unable to perform the simple test of wrist flexion. The other patients in this group were akinetic with varying degrees of rigidity and exhibited only occasional chorea of the limbs, face and trunk. Three of these 4 akinetic patients were taking neuroleptic drugs (pimozide, tetrabenazine and thiopropazate), but the fourth was on no treatment.

Six patients (Cases 5–10) had mild chorea which, in general, did not interfere with their ability to perform simple tasks; all managed daily activities at home and were independent with some assistance. One was taking a neuroleptic (sulpiride), 3 were on baclofen and 2 were untreated.

Seven patients (Cases 11–17) had severe chorea, and were significantly disabled. They experienced considerable difficulty in performing most voluntary movements, but were able to cooperate with the test procedures. All these patients were taking neuroleptic drugs (pimozide, tetrabenzine and tiapride).

Nine of the 11 patients with severe chorea or akinesia required nursing care for daily activities.

For comparison, the simple wrist movements of a group of 8 normal subjects aged 30 to 63 yrs (mean 47 yrs), the complex movements of 9 normal subjects aged 31 to 67 yrs (mean 47 yrs), the stretch reflexes from 12 normal subjects aged 30 to 69 yrs (mean 44 yrs) and the somatosensory evoked potentials from 11 normal subjects aged 28 to 65 yrs (mean 40 yrs) were studied.

### *Methods*

To analyse the distribution, pattern and duration of choreic movements, surface electromyographic (EMG) activity was recorded from different limb muscles including the thenar, flexor and extensor muscles in the forearm, biceps, triceps, tibialis anterior and triceps surae muscles. Recordings were obtained when the subjects were at rest, and while they were performing a motor task or maintaining a posture.

Surface EMG recordings were made using bipolar silver/silver chloride surface electrodes placed over the bellies of the muscles. The signals were preamplified (Devices 3160 band-width from 80 Hz–2.5 kHz, 3 dB points) then amplified (Devices 3120 amplifier) and recorded by a PDP 12 computer using a sampling rate of 500 Hz per channel.

### *Simple movements*

Rapid wrist movements were studied while the patients were seated comfortably in a chair with their forearm held semipronated and strapped to a platform at their side, with the fingers encased in a rigid splint. The mechanical consequences of the movement were monitored by a potentiometer, mounted coaxially with the wrist joint, which signalled the angular position of the wrist. The angular velocity of wrist movement was obtained by analogue differentiation of the position signal. Rectified EMG activity was recorded from the extensor and flexor muscles in the forearm.

The subjects were asked to make rapid wrist flexion movements of 15° and 60° in their own time starting from an initial joint angle of 30° wrist extension. Wrist and target positions were displayed on an oscilloscope in front of the patients who were instructed to align the two marker spots as rapidly as possible. Accuracy was not stressed.

Because of the variability of the patients' movements from trial to trial, and the difficulty in separating voluntary activity from chorea, 20–30 single movements to 15° and 60° targets were recorded from each patient. Out of these, 10 or so trials from each patient were selected in which the onset of the movement was clear (*see* fig. 3 for examples) and the onset and duration of agonist EMG activity was easily identified. In 3 patients this was not possible and the movements were not measured. These selected trials were then used for comparison with results from control subjects. The amplitudes and velocities of the movements were measured, and the duration of the EMG bursts in the agonist muscle was measured from the rectified EMG records by visual inspection.

The total group of patients was compared with the normal age-matched control group of subjects. In addition, the individual subgroups of patients identified on clinical grounds according to the severity of chorea (akinetic, mild-moderate and severe) were compared with each other and with the normal subjects. A separate grouping of the patients with chorea also was undertaken with respect to the medications they were receiving. Those patients with chorea who were receiving neuroleptic drugs, and who were able to perform the simple movements ($n = 5$), were compared with those who were not receiving such medications ($n = 5$). Comparison of groups using data combined from both 15° and 60° movements was made using a two-way analysis of variance (ANOVA) for repeated measures. The coefficient of variation for the position and velocity measurements (1 SD/mean) for patients compared with controls was made using Student's t test.

### *Complex movements*

In selected patients (Cases 4, 5, 7, 9, 10, 13) a more complicated series of movements was examined. These patients exhibited varying degrees of severity of chorea. One was relatively akinetic; 4 others had mild to moderate chorea and 1 had severe chorea. Two were not taking any drugs; 3 were taking baclofen only and 1 took pimozide.

The experimental procedure for examination of simultaneous and sequential movements has been described in detail previously (Benecke *et al.*, 1986, 1987). Briefly, patients were seated with their right arm abducted at 90° at the shoulder. The forearm rested on a manipulandum coaxial with the elbow joint. Angular position of the elbow was monitored by a potentiometer attached to the pivot of the manipulandum. A strain gauge was attached to a U-shaped metal bar at the end of the manipulandum and was grasped between the thumb and fingers. The different movements studied were as follows: single flexions of the elbow through an angle of 15° from a starting angle of 135° ('flex'); single squeezes of the strain gauge to exert a force of 30 N ('squeeze'); both these tasks at the same time ('squeeze and flex'); and both tasks in sequence ('squeeze then flex'). The patients were instructed to perform each movement as rapidly as possible. For the sequential movements the patients were instructed to perform the squeeze movement and immediately on completion of this, flex their elbow.

The elbow position and force of grip were displayed as two vertical bars on an oscilloscope screen in front of the patient. After a series of practice trials 10 single trials of each task were collected. Trials were excluded from analysis if they were not simultaneous or sequential, or if the movements were performed in the wrong order. The movements were carefully monitored by an observer and those which appeared to have been contaminated or interrupted by chorea were excluded from the analysis

EMG activity was monitored in the biceps and opponens pollicis muscles in the manner described above. The velocity of the elbow movement (electronically derived from the position signal), the force of hand squeeze, and rectified EMG were recorded as above. For the sequential movement tasks, the interval between the onset of the first and second movement (the interonset latency, IOL) was also measured. This time includes the duration of the first movement. In order to exclude the contribution of prolongation of the first movement time to the IOL, the movement time of the first movement was subtracted from the IOL, to give an indication of the pause between the two movements.

For the complex simultaneous and sequential movements, the movement times for the elbow flexion movement were compared by Student's t test with those from the group of normal control subjects when the movements was performed alone and as part of a complex movement.

### *Stretch reflexes*

The stretch reflexes in the forearm flexor muscles were studied using the same device described for the ballistic wrist movements, with the forearm semipronated and strapped to a platform. The subjects were requested to maintain a constant position of their wrist (160° flexion) against a background torque (0 25 Nm) produced by a torque motor (Printed Motor G12M). Muscle stretches were given every 5 s by a sudden increase in motor torque to 1 Nm and 1.5 Nm The duration of the imposed displacement was 200 ms

The general method for analysing the stretch reflexes in the flexor pollicis longus has been described in detail previously (Marsden *et al.*, 1976) The proximal phalanx of the thumb was clamped, allowing movements only of the interphalangeal joint, with the pad of the thumb resting on a lever attached to the spindle of a torque motor (Printed Motor G9M4H). Thumb angular position was given by a potentiometer mounted on the motor shaft. EMG activity was recorded by surface electrodes from the flexor pollicis longus muscle. The subjects were requested to maintain a constant thumb position against a background torque 0 07 Nm. Muscle stretches were produced by sudden increase in motor torque to 0.14 and to 0.21 Nm The duration of the stretches was 200 ms and stretches were applied every 5 s.

For both the forearm and thumb stretches, the average of 32 trials was recorded, and the latency and the duration of both the short and long latency EMG reflexes were measured. The size of the reflex was obtained by integrating the rectified EMG activity and expressing it as the percentage increase in activity over baseline levels obtained from control trials in which no stretch was applied. The stretch reflexes were compared with those from a control group of 12 subjects by Student's t test

### *Cortical somatosensory evoked potentials*

SEPs were recorded from electrodes placed over the contralateral scalp, 2 cm posterior to C3 and C4 (International 10/20 system) with reference to Fz, after electrical stimulation of the median nerve at the wrist, just above motor threshold. Recordings were also made from electrodes placed over Erb's point and the neck at the level of C4. In each patient, two series of 1000 responses were averaged, with filters 3 dB down at 80 and 2.5 kHz. The amplitude of the N1 (N20) component of the primary cortical response was measured in two ways· from baseline to peak, and from the N1 peak to the following positive peak (referred to here as P1). The amplitude of the following negative wave was also measured (P1–N2).

The latency values were compared with the normal group by Student's t test The amplitude measurements were complicated by the fact that in some patients there was no detectable primary component of the SEP. When comparisons were made including these zero values, a Mann-Whitney U test was used; otherwise the data were transformed logarithmically to obtain a normal distribution, and compared using Student's t test (Lüders, 1970).

Spearman rank correlation coefficients between the sizes of the individual components of the cortical evoked potential and the size of the stretch reflexes also were calculated. Finally, the velocity of 60° wrist movements was chosen as a measure of motor performance to see if any correlation existed between the sensory evoked potentials, stretch reflexes and movement performance. Spearman rank correlation coefficients were calculated.

## RESULTS

### *Simple voluntary movements*

Normal subjects performed rapid voluntary wrist flexion movements with a biphasic or triphasic patern of EMG activity in the agonist and antagonist muscles. Movements of larger amplitude were accomplished with a greater angular velocity. These were produced by an agonist burst that was larger in size and slightly longer in duration than that for smaller movements (*see* Hallett and Marsden, 1979; Berardelli *et al.*, 1984).

Thirteen of the patients studied were able to perform the task satisfactorily so as to achieve movements of 15° or 60°; in all these patients it was possible to measure the EMG activity in the agonist muscle and its mechanical consquences,

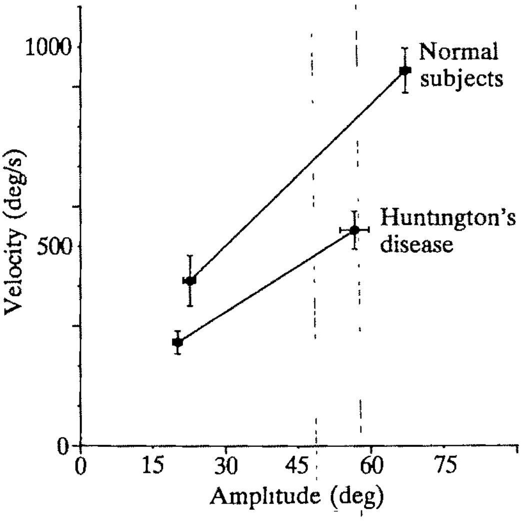

FIG. 1 Mean (± 1 SE) angular velocity and amplitude of voluntary wrist movements in 8 normal subjects and 13 patients with Huntington's disease when attempting to flex the wrist through 15° and 60°

defined by the movement amplitudes and the angular wrist velocity. In 4 patients it was not possible to make such measurements because of considerable irregularity and variability of the movement trajectory, with poor definition of the onset and duration of the agonist EMG burst.

The mean angular velocities in the 13 patients for both large and small amplitude wrist movements were slower than normal (ANOVA at 15° and 60° F (1, 19) = 25.87, $P < 0.001$) (fig. 1). In addition, this analysis revealed a small but significant interaction between angular wrist velocity and wrist position (F (1, 19) = 8.08, $P < 0.05$). This suggested that the relationship between velocity and intended wrist position

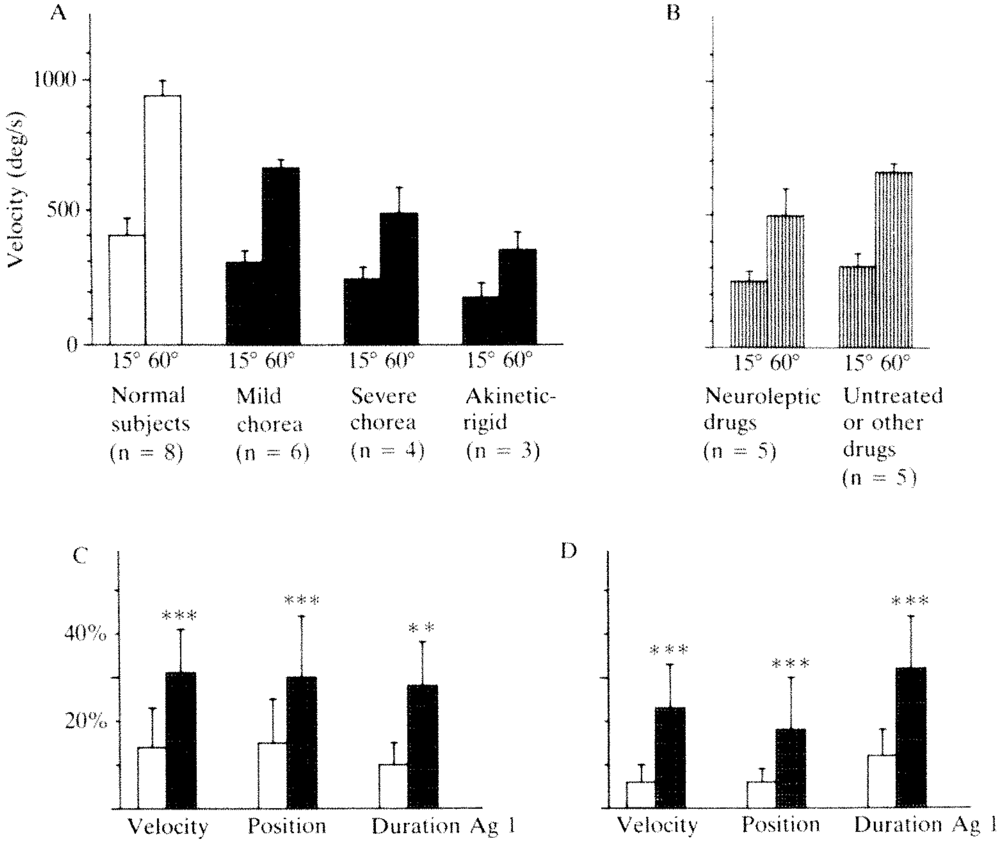

FIG. 2. A, mean (± 1 SE) angular velocity of voluntary wrist flexion movements of amplitudes 15° and 60° in 8 normal subjects (open bars) and 13 patients with Huntington's disease (hatched bars). The latter have been separated into subgroups according to their clinical signs; the wrist movements in all 3 groups were slower than normal and those in the akinetic-rigid group were slower than in the mild group (ANOVA, $P < 0.01$). B, speed of wrist movements in the group of patients with chorea (n = 10) who were receiving neuroleptic drugs (n = 5). This was not significantly different ($P > 0.05$) from those who were untreated or taking baclofen (n = 5); both these groups also were slower than normal (ANOVA, $P < 0.01$). C, D, variability in angular velocity, final position (amplitude of movement) and duration of the first agonist EMG burst (Ag1) for wrist flexion movements of 15° (C) and 60° (D) for normal subjects (n = 8) (open bars) and patients with Huntington's disease (n = 13) (hatched bars), expressed as the mean (± 1SD) coefficient of variation (SD/mean). The coefficient of variation in the patients for each measurement of movement performance was significantly different from normal subjects, indicating a greater variability (Student's t test: $^{**}P < 0.01$; $^{***}P < 0.001$).

in the patients differed from that in normal subjects. The angular velocities for both amplitudes of movement were slower than normal when compared by Student's t test (15°, $P<0.05$); 60°, $P<0.001$). When the individual groups of patients were considered, movement speed was slower than normal in each category (fig. 2A); those patients who were rigid and relatively akinetic were slower in comparison with those who had mild chorea (ANOVA at 15° and 60°, $F(1, 7)=13.95$, $P<0.01$) (fig. 2A). Among the patients with chorea (mild or severe) ($n=10$), the speed of movements of those receiving neuroleptic medications ($n=5$) was not significantly

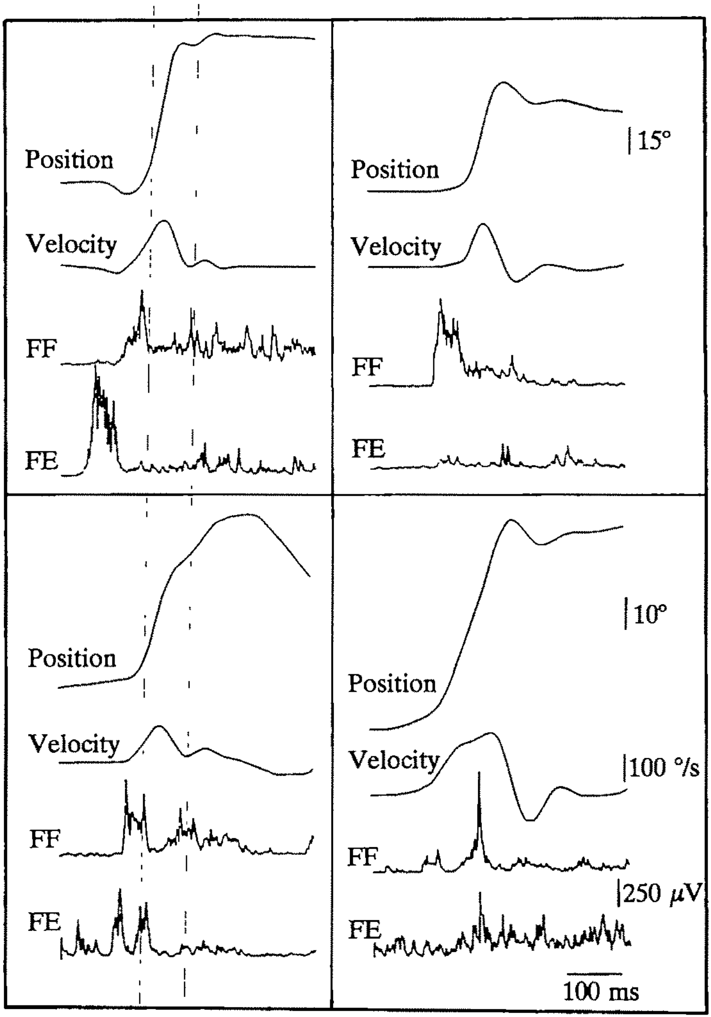

FIG. 3. Wrist position, angular velocity, and rectified EMG traces from forearm flexor (FF) and extensor muscles (FE) during 4 separate voluntary wrist movements attempting to reach 60° in a 46-yr-old patient with a 14 yr history of Huntington's disease (*Case 14*). The patient had severe chorea and was taking tetrabenazine and pimozide. The 4 movements illustrate the variable movement trajectory and patterns of agonist and antagonist muscle activation during consecutive movements. Only the movements in the *upper right* and *lower left* panels would have been measured from these trials, as the wrist position in the *upper left* panel was displaced by chorea before the onset of wrist flexion; in the *lower right* panel, the onset of the movement is not clear.

different to those who were receiving baclofen or no drugs (n = 5) (ANOVA at 15° and 60°, F (1, 8) = 2.57, $P > 0.05$) (fig. 2B).

The mean data of fig. 1 obscure the variability seen from trial to trial in each subject. In fact, the variability in peak velocity and end position was far greater in the patients than in normal subjects (fig. 2C, D).

A biphasic pattern of EMG activity in agonist and antagonist muscles which is typical of rapid wrist movements in normal subjects, was seen only in the group of patients with mild chorea. Those patients with severe chorea and those who were akinetic exhibited a variety of combinations of EMG activity, in which the the agonist burst varied from trial to trial (fig. 3). This degree of variability was greater than that seen in normal subjects.

The mean duration of the first agonist burst for all 13 patients was not significantly different from that in normal subjects (not illustrated). However, the duration of the first agonist burst in patients who were rigid was prolonged when compared with normal subjects (ANOVA at 15° and 60°, F (1, 9) = 15.14, $P < 0.01$) (fig. 4). Similarly, prolongation of the first agonist burst also was present in those patients with severe chorea compared with normal subjects (ANOVA at 15° and 60°, F (1,10) = 6.52, $P < 0.05$) (fig. 4). There was no difference in the duration of the first agonist burst in those patients with chorea who were receiving neuroleptic drugs and those who were not (ANOVA at 15° and 60°, F (1,8) = 1.72, $P > 0.05$). The duration of the first agonist burst was highly variable in all patients (fig. 2C, D).

In 3 patients (Cases 15–17) with severe chorea in whom it was not possible to measure the EMG activity, a well defined agonist burst, representing the intial component of the normal biphasic pattern of agonist and antagonist muscle

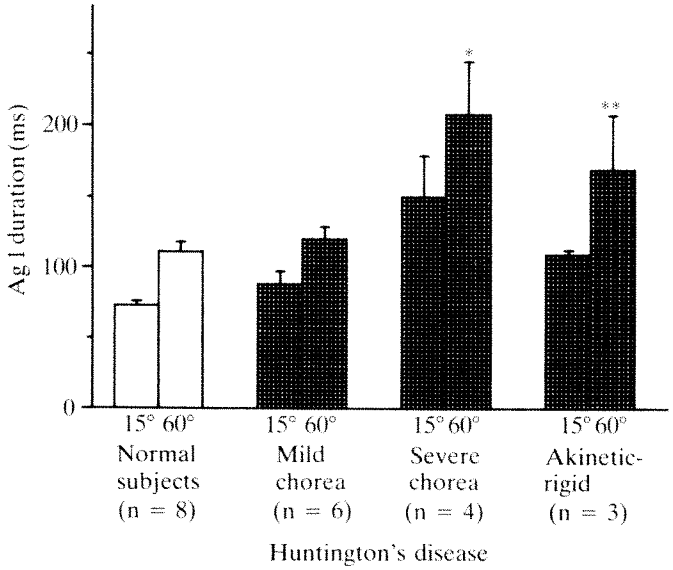

FIG. 4. Mean (± 1 SE) duration of first agonist burst (Ag1) in wrist flexor muscles during wrist flexion movements of amplitudes 15° and 60° in 8 normal subjects (open bars) and 13 patients with Huntington's disease (hatched bars). The patients have been divided on clinical grounds into three groups. The Ag1 duration of akinetic-rigid patients and patients with severe chorea were longer than normal (for comparison of the duration of Ag1 for 15° and 60° movements in patients versus normal subjects (ANOVA): $^*P < 0.05$, $^{**}P < 0.01$).

activation, was only seen occasionally. The agonist burst was often poorly defined, varying from a single prolonged and dispersed burst of activity to repeated smaller bursts. Activity in the agonist muscle occurred both in isolation and in combination with an antagonist burst of variable timing, either cocontracting or starting before or after the agonist. These different patterns could be recorded in the same patient on successive trials.

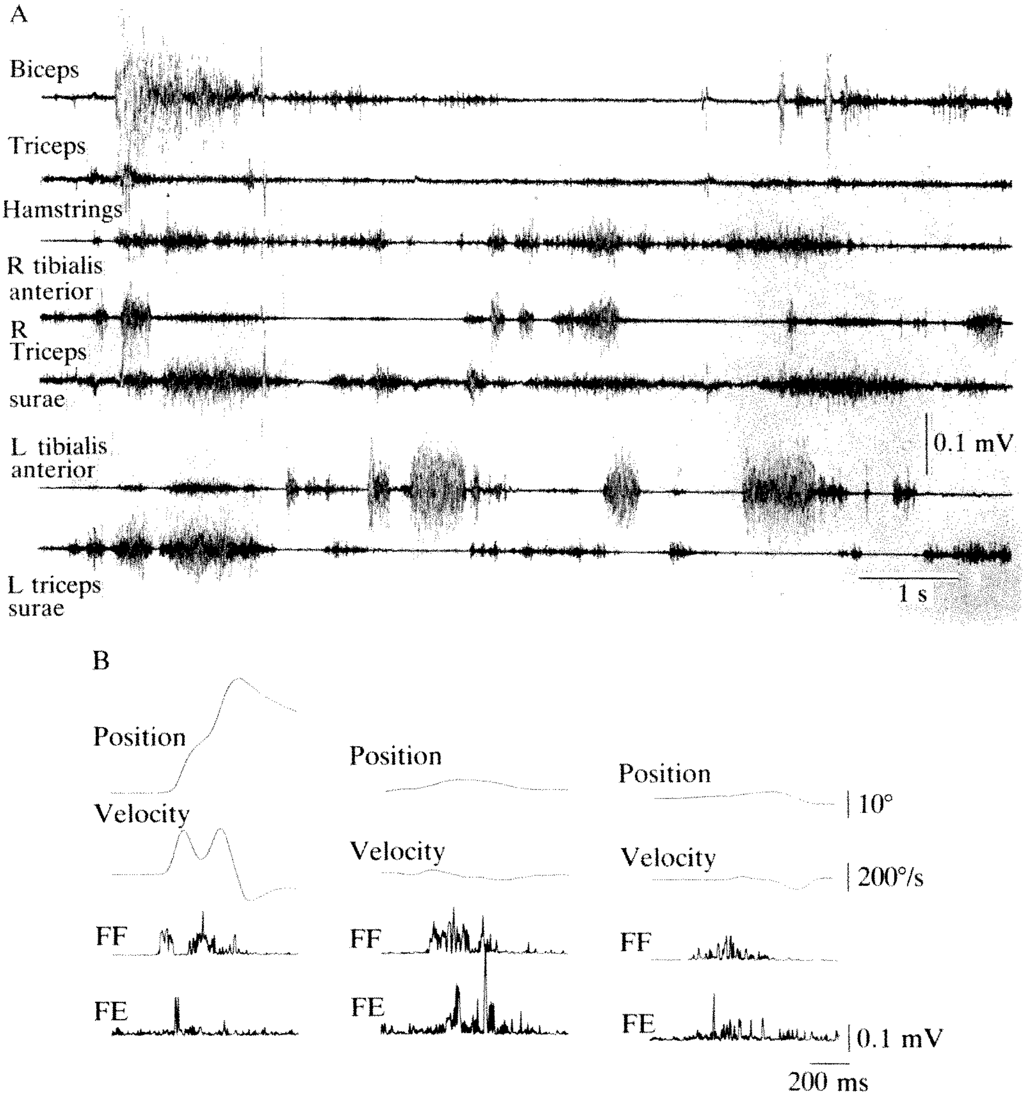

FIG. 5A. EMG recordings from a variety of muscles in a 60-yr-old man with Huntington's disease and mild chorea (*Case 7*), while seated, illustrating the random pattern of muscle activation and variable EMG burst length of chorea. FIG. B, wrist position, angular wrist velocity traces and rectified EMG signals from forearm flexor (FF) and extensor (FE) muscles in a 40-yr-old woman with Huntington's disease illustrating a choreic burst interrupting an attempted voluntary wrist flexion movement to 15° (*left panel*) and spontaneous choreic movement producing a small amplitude movement (*middle and right panel*).

### *Involuntary movements*

The EMG activity corresponding to spontaneous chorea was characterized by a random flow from one muscle group to another, and a highly variable duration of the individual choreic bursts. The duration of the great majority of choreic bursts ranged from 200 to 400 ms. However, a wide spectrum was present with short, discrete bursts of the order of 50 to 200 ms duration and prolonged contractions lasting up to 2 s (fig. 5A).

In 3 patients (Cases 4, 11, 13) it was possible to compare spontaneous choreic movements of the wrist with those produced by voluntary activity. The EMG activity in the forearm muscles during these spontaneous movements consisted of long cocontracting bursts in the agonist and antagonists (fig. 5B). These cocontractions produced movements of only small amplitude (1° to 20°). The angular velocity of these movements (20 to 400 deg/s) were comparable with speeds of voluntary movements for similar amplitudes in the same patients. The mean angular velocity of voluntary simple wrist flexion movements in the same patients varied from 15 to 336 deg/s. Often it appeared as if chorea interfered with the execution of normal voluntary movements. For example in fig. 5B, there was an initial correct movement to 15°, which was followed by an additional EMG burst which took the wrist beyond the target. In other subjects, the opposite occurred: a large antagonist burst displaced the wrist in the direction opposite to the target.

### *Complex voluntary movements*

The two types of complex voluntary movements studied were (1) simultaneous isotonic flexion of the elbow and isometric squeeze of a force transducer, and (2) a sequential movement of squeeze followed by flexion. As with the simple wrist flexion task, all movements were self-paced and executed with the instruction to be made as fast as possible.

*Simultaneous flex and squeeze.* Normal subjects performed this simultaneous movement task with ease. The peak velocity and timing of the individual components of flex and squeeze were the same as when the individual movements were performed separately (fig. 6).

Of the 6 patients who were examined (1 was receiving a neuroleptic drug), only 2 performed as normal. When each component (flex and squeeze) was carried out separately by these 2 patients, their individual movements were as fast as normal. Their peak velocity and movement time did not change when the two movements were executed simultaneously. These patients (Cases 7, 10) had mild chorea with little functional impairment (both were taking baclofen).

In the remaining patients (Cases 4, 5, 9, 13), the movement times for the simple single squeeze movement were prolonged (mean (± 1 SD) movement time 406 ± 132 ms; normal subjects 156 ± 23 ms, $P < 0.001$), as were those for simple single elbow flexion (mean movement time 399 ± 124 ms; normal subjects 229 ± 41 ms, $P < 0.001$). When performed simultaneously, the squeeze movement

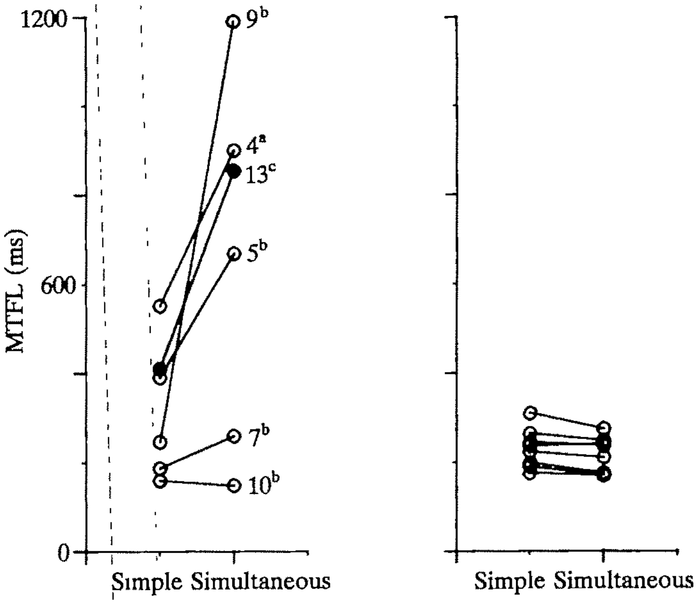

FIG 6. Movement times for elbow flexion (MTFL) in 10 normal subjects (*right hand panel*) and 6 patients with Huntington's disease (*left hand panel*) when performed alone (simple) and simultaneously with a squeeze movement of the hand (simultaneous) In 4 of the 6 patients with Huntington's disease, performance of the simultaneous task led to a marked slowing and prolongation of the elbow flexion movement time Normal subjects (and 2 patients) were able to perform the simultaneous task without any decay in movement times. One patient was receiving a neuroleptic drug, pimozide, and is shown by solid symbols; 3 others were taking baclofen and 2 were untreated [a] akinetic-rigid, [b] mild chorea; [c] severe chorea.

time remained unchanged, but the elbow flexion movement became slower and the movement time increased (from 399 ± 124 ms to 904 ± 216 ms, $P < 0.001$). Two of these patients (Cases 5, 9) had mild chorea, 1 of whom (Case 5) was receiving baclofen; 1 had severe chorea (Case 13) and was receiving pimozide, and 1 was akinetic and rigid on no therapy (Case 4).

*Sequential squeeze then flex.* Normal subjects executed each component movement of this task as rapidly as when each movement was made separately. There was a slight pause between the completion of squeeze and the onset of the flex movement lasting 94 ± 12 ms; the mean interonset latency between the movements was 244 ± 33 ms.

When attempting to perform sequential movements, profound difficulties were observed in the 5 patients studied (Cases 4, 5, 7, 9, 13). All found this task difficult to learn. One patient (Case 9) with mild to moderate chorea, who was not on treatment, was unable to perform the task, while another (Case 7), again with mild to moderate chorea and only taking baclofen, could only perform the two movements simultaneously. The remaining 3 patients (Case 4 on no treatment, Case 5 only taking baclofen, and Case 13 on pimozide) had squeeze movement times that were the same as those when this movement was performed alone. However, the elbow flexion movement times in the sequence exceeded those when this movement was performed alone (by 226, 68 and 1007 ms, respectively). The

IOL between the two movements of the sequence was significantly longer in these subjects (452, 504 and 628 ms, respectively; mean 528 ± 90 ms) than in normals (244 ± 33 ms, $P < 0.001$), as was the pause (223, 190 and 244 ms, respectively; mean 219 ± 27 ms) as compared to normals (94 ± 12 ms, $P < 0.001$).

### *Stretch reflexes*

*Wrist flexors.* The average latency, duration and size of the short and long-latency components of the stretch reflexes in the flexors of the wrist obtained in the 12 normal subjects and the 17 patients with Huntington's disease are shown in fig. 7. Short-latency reflexes were present in all normal subjects and patients, and long-latency responses were present in all normal subjects, and in 15 of the 17 patients. Both patients in whom the reflex was absent had severe chorea.

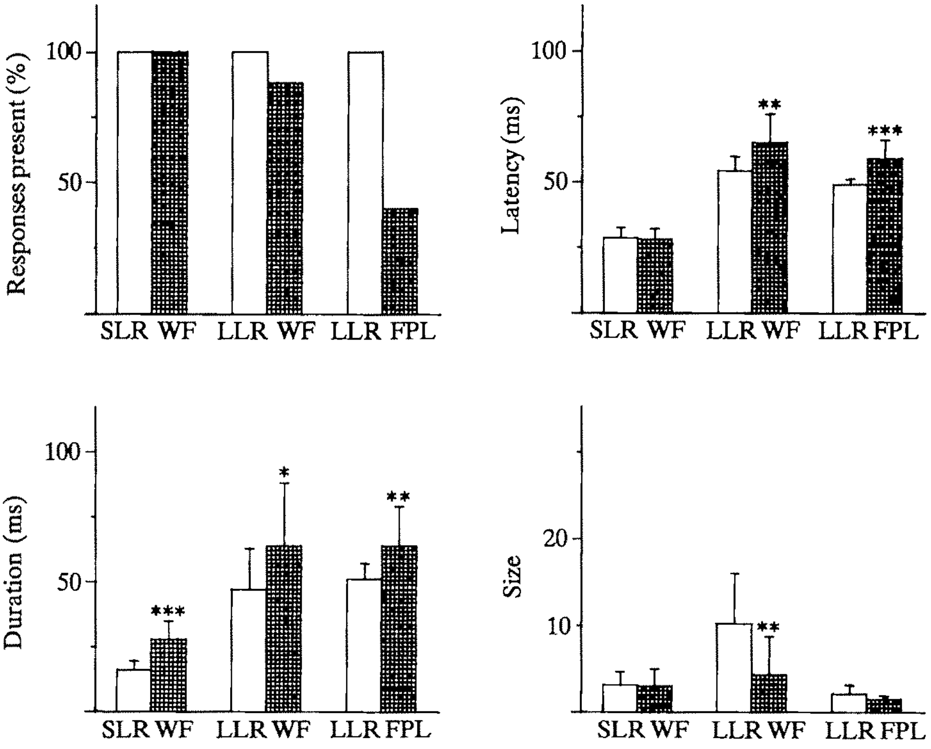

FIG 7 Mean (± 1SD) size, duration and latency of short (SLR) and long-latency (LLR) stretch reflexes in wrist flexor muscles (WF), and long-latency stretch reflexes (LLR) in flexor pollicis longus (FPL) in normal subjects (open bars) and patients with Huntington's disease (hatched bars) Short-latency EMG responses to stretch were present in the flexor muscles of all normal subjects (n = 12) and patients (n = 17), long-latency responses were present in all normal subjects in both the wrist flexors and flexor pollicis longus, but were absent in the wrist flexor muscles in 2 patients and in flexor pollicis longus in 9 of the 15 patients in whom it was possible to examine this reflex (*upper left panel*) The latency of the long-latency reflexes in the wrist flexor and flexor pollicis longus muscles were longer than normal (*upper right panel*), and the duration of both short and long-latency stretch reflexes were prolonged (*lower left panel*) in patients with Huntington's disease. The size of the long-latency components were smaller than normal (*lower right panel*) but this was significant only for the wrist flexors. Response size has been expressed as the fractional increase in EMG activity above baseline $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$).

The size and latency of the short latency responses in patients were similar to normal, but their duration was prolonged ($P < 0.01$). The mean size of the long-latency responses was smaller than normal ($P < 0.01$) while the mean duration ($P < 0.05$) and mean latency ($P < 0.01$) were prolonged in patients. The duration of the long-latency reflex was longer in patients with mild and severe chorea than in those who were akinetic and rigid (akinetic-rigid vs mild chorea, $P < 0.05$; akinetic-rigid vs severe chorea, $P < 0.01$). There was no difference in the size or latency of the reflexes between the patients with respect to medication.

*Flexor pollicis longus.* Short-latency stretch reflexes cannot be obtained from the thumb in many normal subjects, so only long-latency reflexes (which were present in all normal subjects) are considered. Two patients (Cases 1,17) were unable to maintain a constant position of the thumb. In 9 patients (Cases 6, 7, 9–11, 13–16) the long-latency EMG responses were absent, although they had been present in the wrist flexors in 7 of these patients. In 6 other patients (Cases 2–5, 8, 12) long-latency reflexes in flexor pollicis longus were present; with one exception, these patients had mild chorea or were akinetic and rigid.

The average latency, duration and amplitude of the long-latency EMG response to stretch of the flexor pollicis longus in normal subjects and in the 6 patients with Huntington's disease are shown in fig. 7. In those in whom the reflex was present the latency was delayed ($P < 0.001$), and the mean duration was prolonged in comparison with normal subjects ($P < 0.05$), but there was no difference in the size of the response ($P < 0.05$). There were insufficient numbers to allow a comparison of the patients with and without drugs.

### *Cortical somatosensory evoked potentials*

The first 3 components of the cortical SEP (N1, N1-P1, P1-N2, *see* Methods) following median nerve stimulation at the wrist were examined in 16 of the 17 patients. Potentials recorded over Erb's point and the cervical spinal cord were of normal latency (Erb's point 9.8 ± 0.9 ms (mean ± 1SD); normal 10 ± 0.6 ms; cervical spine 13.2 ± 1.3 ms; normal 13.3 ± 0.8 ms). No cortical response could be distinguished in 7 patients (Cases 2, 10, 13–17). The sizes of all 3 components of the cortical SEPs in the total group of patients were significantly smaller than normal (Mann-Whitney test, $P < 0.05$). In 9 patients (Cases 1, 3–9, 11, 12) in whom a cortical potential was obtained the mean N1 latency was normal (19.8 ± 1.7 ms; normal 18.9 ± 0.7 ms), but the size of N1 and N1-P1 components were smaller than normal (Student's t test on the logarithmically transformed data, $P < 0.002$). However, the amplitude of the P1-N2 component was the same in both groups ($P > 0.05$) (Table 2).

As was noted with the long latency stretch reflex in the thumb flexor, the cortical SEP was absent in most patients with severe chorea (Table 1). However, using a $\chi^2$ analysis, there was no association between the presence or absence of the long-latency stretch reflex in flexor pollicis longus and the SEP ($\chi^2 = 1.7$, df $= 1$, $P > 0.05$).

TABLE 2 SUMMARY OF SEP LATENCY AND AMPLITUDE MEASUREMENTS THE AMPLITUDE (MEAN ± 1 SD) OF THE SEP COMPONENTS GIVEN FOR THE 9 PATIENTS IN WHOM SEP WAS PRESENT*

| | *Normal subjects* (*n* = *11*) | *Huntington's disease* (*n* = *9*) |
|---|---|---|
| N1 latency (ms) | 18.9±0.7 | 19.8±1.7 |
| Amplitude | | |
| N1 | | |
| μV | 1.4±0.8 | 0.34±.33 |
| Log | 0.0904±0.2444 | −0.5431±0.4892** |
| N1-P1 | | |
| μV | 2.8±1.2 | 1.3±1.2 |
| Log | 0.4013±0.2113 | −0.1087±0.2684** |
| P1-N2 | | |
| μV | 1.9±1.1 | 2.1±2.4 |
| Log | 0.2476±0.1924 | 0.2312±0.3964 |

* For details of SEP component labelling and indentification, *see* Methods
** $P<0.002$

We then sought to investigate whether the size of the long-latency stretch reflexes in each muscle were related to the size of the SEP components, but no relationship could be found (Spearman rank correlation coefficients ($\rho$): size of long-latency stretch reflex in wrist flexors (n = 16) vs size N1, $\rho=0.1$; vs size N1-P1, $\rho=0.01$; vs size P1-N2, $\rho=0.02$; size of long-latency stretch reflex in flexor pollicis longus (n = 14) vs size N1, $\rho=0.5$; vs size N1-P1, $\rho=0.4$; vs size P1-N2, $\rho=0.4$; $P>0.05$ for all values).

There was a marginal association between the presence or absence of the long-latency stretch reflex in flexor pollicis longus and the clinical assessment of chorea in the 3 groups of patients ($\chi^2=5.97$, df = 2; $P=0.05$), but none was evident for the SEP ($\chi^2=3.1$, df = 2, $P>0.05$).

Finally, we attempted to test whether there was any correlation between the SEP, long-latency stretch reflexes and the speed of voluntary movements in individual patients. There was no correlation between any component of the SEP or of the size of the stretch reflex in wrist and thumb flexors and the peak velocity of a 60° wrist flexion movement (Spearman rank correlation coefficients ($\rho$): velocity (n = 12) vs size N1, $\rho=0.2$; vs size N1-P1, $\rho=0.1$; vs size P1-N2, $\rho=0.1$: velocity vs size wrist flexor long-latency stretch reflex, $\rho=0.2$; vs size flexor pollicis longus long-latency stretch reflex, $\rho=0.3$: $P>0.05$ for all measurements).

## DISCUSSION

The present experiments revealed abnormalities of motor control and the processing of sensory information in patients with Huntington's disease. The latter have been well documented previously, but it has not been clear whether or how they might be related to the major clinical motor manifestations of the disease. The problems that are encountered in interpreting these findings are addressed below, followed by a discussion of the new findings in this study concerning the control of voluntary movement.

### *Sensory processing in Huntington's disease*

The changes that we have documented in the long-latency stretch reflex and in the somatosensory evoked potentials are very similar to those described previously (*see* Ehle *et al.*, 1984; Noth *et al.*, 1984; Bollen *et al.*, 1985). Both the primary component (baseline – N1 peak, or N1-P1) of the median nerve evoked potential, and the long-latency stretch reflex in forearm muscles, tended to be reduced in size or absent in patients with Huntington's disease. In addition, we have shown (1) that the effect on the long-latency stretch reflex is greater on the long flexor of the thumb than on the flexor muscles of the wrist in the forearm, and (2) that although the primary component of the SEP is abnormal, the later P1-N2 peak may be unaffected in the patient group.

The reasons for these electrophysiological abnormalities are not known in detail. Absence of the N1 component of the SEP may reflect a failure or a desynchronization of the afferent input reaching the cerebral cortex. This must be presumed to occur above the level of the generators of the spinal SEP components as these were normal, and could result from pathological processes affecting the cortex (Bollen *et al.*, 1985) or thalamus (Ehle *et al.*, 1984), both of which are known to be involved in Huntington's disease. If the P1-N2 component of the SEP is due to later long-term processing of the input responsible for the N1 peak, then desynchronization of the primary input might have less effect on the P1-N2 response and account for its relative preservation in the patients.

Absence or reduction of the long-latency component of the stretch reflex might also be compatible with changes in sensory input to cortex. If a long loop transcortical reflex pathway does contribute to the long-latency stretch reflex (Marsden *et al.*, 1983*a*), then it would not be surprising to find that the reflex is reduced in a group of patients with evidence of abnormal sensory input to cortex. The hypothesis that the transcortical loop plays a more important role in reflex responses of muscles controlling the most distal joints of the hands (*see* Marsden *et al.*, 1983*a*) would also account for the more pronounced changes in the flexor pollicis longus, compared with the wrist flexor stretch reflexes. If these changes in long-latency stretch reflexes are explained by involvement of a transcortical pathway, it might be expected that there would be a correlation between the size of the SEP and the reflex, especially as about 50% of the primary component of the SEP is due to activity in muscle spindle Ia afferent projections (Gandevia *et al.*, 1984). However, the absence of a correlation was not altogether surprising. The reason for this is that the SEP was obtained by stimulation of afferents (median nerve at wrist) which could not have contributed to the stretch reflex of the muscles studied. Ideally, the SEP should be recorded in response to stretch of a single muscle and correlated with the resulting long-latency stretch reflex in the same muscle.

Despite the relatively clear abnormalities in the SEP and stretch reflex, we still do not know how they relate to the difficulties experienced in voluntary movement in Huntington's disease. Neither the long-latency stretch reflex nor the SEP changes were significantly correlated with measures of voluntary movement or the clinical grouping of the patients (mild chorea, severe chorea or akinetic-rigid). They appeared to be epiphenomena of the disease process rather than casual factors in the clinical picture. However, the numbers of patients in each group were small; correlations between electrophysiological abnormalities and clinical symptoms may become apparent in future studies with larger groups of patients. One possibility is that the size of the long-latency stretch reflex might be related to the muscle tone in Huntington's disease, as it is in Parkinson's disease (Lee and Tatton, 1975; Rothwell *et al.*, 1983). If so, it would pose an interesting question for longitudinal study: do patients who lose the long-latency stretch reflex in the mild to moderate middle stages of the disease regain it during the final rigid phase? Or do patients who become rigid belong to a separate group of individuals who never lose their stretch reflex?

### *Voluntary movement in Huntington's disease*

Three major abnormalities of voluntary arm movement in patients with Huntington's disease were studied. (1) The maximum speed of voluntary wrist flexion was reduced compared with normal subjects. Hefter *et al.* (1987) have reported a similar slowness of rapid finger movements in Huntington's disease. Such slowness of movement attempted at maximum velocity was most obvious in akinetic-rigid patients, but was also seen in those with chorea alone. It was not due to the effects of neuroleptic treatment; those patients who were receiving medication moved as fast as those who were drug free. (2) Combined simultaneous or sequential movements of 'squeeze' of the hand and 'flex' of the elbow were even more affected. Many patients were unable to execute such movements. In those who could, the speed of elbow flexion often was further reduced when executed at the same time or shortly after a hand squeeze. Similarly, the pause between component movements during the sequential task was longer than normal. These defects of complex movements were seen in those with chorea alone, and in those not taking neuroleptic drugs. (3) All voluntary movements to a target were more variable in both the final end position and the peak velocity than the movements of normal subjects.

### *Bradykinesia in Huntington's disease*

The first two deficits are very similar to those seen in patients with Parkinson's disease, and reflect an underlying bradykinesia in Huntington's disease. Not surprisingly, the degree of bradykinesia was greatest in patients who were akinetic and rigid, but it was also seen in those with chorea alone, especially those with severe chorea. Such bradykinesia occurred in those not taking neuroleptic drugs, so cannot be attributed to drug-induced parkinsonism. We conclude that bradykinesia is a fundamental feature of the motor deficits of Huntington's disease, even in those who clinically appear only to have chorea.

Clinical studies of Huntington's disease indicate that difficulties with voluntary movement become more pronounced as chorea subsides and bradykinesia becomes more evident. This would explain why neuroleptic treatment may produce little improvement in functional ability despite pronounced effects on chorea (Shoulson, 1981; Girotti *et al.*, 1984; Quinn and Marsden, 1984; Koller and Trimble, 1985). Indeed neuroleptic therapy may make matters worse by exaggerating bradykinesia.

Slowness of fast simple single voluntary movements is characteristic of Parkinson's disease (Hallett and Koshbin, 1980; Berardelli *et al.*, 1986). So too is disruption of complex dual simultaneous and sequential movements (Benecke *et al.*, 1986, 1987). Similar defects of both simple and complex movements were found in Huntington's disease in the present study. In both conditions, complex movements appear more affected than simple tasks. Thus patients with Huntington's or Parkinson's disease are capable of executing simple single movements in the correct direction, albeit more slowly than normal, and can adjust their motor output to achieve movements of different sizes. However, when they attempt to execute more complex simultaneous or sequential motor acts, added difficulties emerge. A further slowing of the second movement appears and its initiation is delayed. This suggests that there is a difficulty in motor programming of complex movements in both diseases, over and above the defect in execution of single simple movements.

Although superficially similar in terms of its effect on movement speed, the detailed mechanism of bradykinesia in Huntington's disease may be different from that in Parkinson's disease. The slowing of voluntary movement in the mild and severe choreic groups was not accompanied by any other clinical signs of parkinsonism. In addition, the EMG patterns recorded during voluntary wrist flexion, even in those patients who were akinetic-rigid (i.e., clinically parkinsonian), were not the same as those seen in Parkinson's disease (Hallett and Khoshbin, 1980; Berardelli *et al.*, 1986). In the latter disorder, the first burst of activity in the agonist is small but of normal duration, in contrast to the prolonged and highly variable EMG bursts of Huntington's disease. Prolonged EMG bursts and variable movement trajectories are more reminiscent of those described in athetosis (Hallett and Alvarez, 1983) and Sydenham's chorea (Hallett and Kaufman, 1981). Nevertheless, despite these detailed differences, the final bradykinesia for both simple and complex simultaneous and sequential movements is remarkably similar in both Huntington's and Parkinson's disease.

The corticomotoneuron pathway appears normal in both Parkinson's and Huntington's disease (Thompson *et al.*, 1986), so the defects of motor programming seen in both conditions probably lies in delivery of abnormal motor instructions to the motor cortex from premotor and supplementary motor cortical areas. Abnormal motor programming in both Parkinson's and Huntington's disease is best interpreted as due to dysfunction of the premotor and supplementary motor cortex consequent upon abnormal input into these areas from the diseased basal ganglia.

Contemporary theories of basal ganglia motor function concentrate upon an input from motor cortex (excitatory) to striatum, a striatal output (inhibitory) to medial globus pallidus and substantia nigra pars reticulata, then pallidal and nigral outputs (inhibitory) to thalamus VA and VL, and thalamic projections (excitatory) to premotor and supplementary motor areas (Kemp and Powell, 1971; Penney and Young, 1983; Alexander *et al.*, 1986). This cortico-striato-pallido/nigro-thalamo-cortical feedback loop is excited by cortical input, and results eventually in facilitation of premotor and supplementary motor cortical activity. In other words, input from the sensorimotor cortex facilitates activity in the premotor areas through this complex basal ganglia motor circuit, which acts as a positive feedback system that might reinforce ongoing motor activity.

Loss of striatal output neurons in Huntington's disease would remove basal ganglia activation of premotor areas. The situation in Parkinson's disease is more complex. At first sight, loss of dopamine inhibition of striatal neurons might be expected to facilitate basal ganglia excitation of the cortex, that is, the opposite of what happens in Huntington's disease. However, recent evidence (*see* Penney and Young, 1986) suggests that the overall effect of dopamine is excitatory to striatal output neurons to medial globus pallidus and substantia nigra reticulata. Accordingly, loss of the dopaminergic nigral pathway to the motor areas of the striatum in Parkinson's disease might have a similar functional effect as the loss of those striatal output neurons in Huntington's disease. The bradykinesia characteristic of Parkinson's disease, and now shown to be a fundamental motor deficit in Huntington's disease, would thus be due to impairment of activity in the cortico-striato-pallido/nigro-thalamo-cortical motor circuit in both conditions, leading to a failure of activation of premotor and supplementary motor cortex.

### *Chorea in Huntington's disease*

The cause of the choreic movements in Huntington's disease remains unknown. The variable duration of the bursts of muscle activity in chorea and their random timing and distribution are well-known clinical characteristics (Wilson, 1925; Hoefer and Putnam, 1940; Hallett and Kaufman, 1981; Marsden *et al.*, 1983*b*). There are therefore no specific EMG characteristics that define individual bursts of EMG activity as chorea: they may be of short duration as in myoclonus, or long as in dystonia (Marsden *et al.*, 1983*b*). In this study we have shown that choreic movements tend to be of small amplitude and of low velocity, similar to voluntary movements of comparable amplitudes in the same patients.

Building upon the critical function of the cortico-striato-pallido/nigro-thalamo-cortical motor circuit in reinforcing motor behaviour, Penney and Young (1983, 1986) have highlighted the parallel role of cortico-striato-pallido-*subthalamo*-pallidal pathways in inhibiting movement. Cortical inputs excite striatal neurons that inhibit lateral globus pallidus, which projects an inhibitory pathway to the subthalamic nucleus. The end effect of this cortical input would be to drive subthalamic activity, reinforced by a direct excitatory corticosubthalamic pathway. It is suggested that the subthalamus projects excitatory pathways to the medial globus pallidus to suppress unwanted movement.

The important role of the subthalamic nucleus in the production of dyskinesias is supported by observations made on lesions in the region of the subthalamic nucleus, which produce contralateral hemiballism or hemichorea (Martin, 1927; Whittier, 1947; Crossman *et al.*, 1984). Injections of bicuculline into the subthalamic nucleus or ventrolateral lentiform nucleus, in the monkey, can produce hemiballism or hemichorea, respectively (Mitchell *et al.*, 1985*a*, *b*). Although the mechanisms responsible for these experimental dyskinesias are unresolved (*see* Crossman, 1987, for recent review), local cerebral metabolic activity after such injections (examined by 2-deoxyglucose autoradiography) in both hemiballism and hemichorea showed changes consistent with decreased activity in subthalamopallidal and pallidothalamic pathways (Mitchell *et al.*, 1985*b*; Crossman, 1987).

Loss of striatal neurons in Huntington's disease would have the same effect, causing disinhibition of lateral globus pallidus projections to the subthalamic nucleus, which would be excessively inhibited. The loss of subthalamic drive to medial pallidal neurons would result in decreased pallidothalamic inhibition causing increased thalamocortical excitation, thereby generating chorea. Although speculative, such a theory predicts that bradykinesia and chorea can coexist, as has been found in the present study.

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# THE NEUROPATHOLOGY OF THE ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS)

## A REVIEW

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## SUMMARY

The nervous system has been involved in the majority (at least 75%), of cases of acquired immune deficiency syndrome (AIDS) examined postmortem, but the pathogenetic mechanisms involved are not well understood. The predominant pathological process is opportunistic infection secondary to the decrease of T-helper (T4) cells and includes toxoplasmosis, encephalitis due to cytomegalovirus and progressive multifocal leucoencephalopathy. On the other hand, mycoses (mainly cryptococcosis) are relatively uncommon Primary lymphomas are three times more common than secondary lymphoma spreading from other sites. Cerebral involvement by Kaposi sarcoma is metastatic, probably from primary foci in the lungs.

Lesions due to the direct involvement of the nervous system by the human immune deficiency virus (HIV) include subacute encephalitis and vacuolar myelopathy The former is reported with increasing frequency and is localized predominantly to the white matter in which multinucleated giant cells can be found. These are considered typical of AIDS and have been shown to contain HIV particles in their cytoplasm.

AIDS lesions due to infectious agents do not always conform to the typical pattern of the uncomplicated disease and not uncommonly there is evidence of more than one infectious agent in the same area.

Peripheral nervous system lesions in HIV infections, responsible for a variety of clinical symptoms, usually appear, in biopsy material, as nonspecific inflammatory in type. CMV inclusions and lymphomatous infiltrations of peripheral nerve have been reported in autopsy cases

## INTRODUCTION

The acquired immune deficiency syndrome (AIDS) is a disease caused by the lymphadenopathy-associated virus LAV (Barré-Sinoussi *et al.*, 1983) or human T cell lymphotropic retrovirus type III (HTLV-III) (Popovic *et al.*, 1984). The virus, now called human immune deficiency virus or HIV (Piszkievicz *et al.*, 1986), has a particular tropism for the protein CD4 contained in T4 lymphocytes (Dalgleish *et al.*, 1984) which are destroyed with consequent loss of cell-mediated immunity.

The spectrum of illnesses in AIDS patients is wide and almost every organ or

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system, including the nervous system, has been found to be involved (Reichert *et al.*, 1983). Since the first report by Snider *et al.* (1983), numerous publications have broadened the knowledge of the neurological complications in this new disease: thus it has been described in children, not only those receiving contaminated blood (Curran *et al.*, 1984), but also those born to parents belonging to one of the risk groups for AIDS (Belman *et al.*, 1985; Scott *et al.*, 1985). Following the initial report of peripheral nerve involvement (Horowitz *et al.*, 1982; Snider *et al.*, 1983) various neuromuscular complications have been described (Dalakas and Pezeshkpour, 1986). The most recent finding of giant cells in the brain (Kleihues *et al.*, 1985; Sharer *et al.*, 1985; Budka, 1986) has also made it necessary to redefine the concept of subacute encephalitis (Snider *et al.*, 1983).

## NEUROPATHOLOGY

Patients with AIDS belong to a variety of risk groups such as homosexual or bisexual individuals, intravenous drug users, patients receiving frequent blood transfusions and Haitians, but cases have been described, in whom none of these risk factors could be identified (Fauci *et al.*, 1985).

It has been reported that 40 to 50% of AIDS patients, including adults and children, have neurological symptoms which, in 10% of the cases, may represent the first manifestation of the disease (Bredesen and Messing, 1983) and that up to 80% of AIDS patients show morphological abnormalities of the nervous system (Snider *et al.*, 1983, Epstein *et al.*, 1985; Levy *et al.*, 1985*b*; Anders *et al.*, 1986; Petito *et al.*, 1986).

### *Involvement of the central nervous system*

#### *Opportunistic infections*

The most frequent type of pathology is due to opportunistic infections and reflects the severe defect in T cell-mediated immunity (Fauci *et al.*, 1984, 1985; Lane *et al.*, 1985).

*Parasitoses.* Cerebral involvement by *Toxoplasma gondii* has been found to be the most common cause of focal brain lesions by Snider *et al.* (1983), Katlama *et al.* (1984), Luft *et al.* (1984), Moskowitz *et al.* (1984*a*) and Hénin *et al.* (1987), as well as by Lucas and Wamukota (1987) in a study of 22 cases examined postmortem from Mulago Hospital, Kampala, Uganda. In the series reported by Petito *et al.* (1986), toxoplasmosis was present in 10.5% of the cases. The characteristic lesions (fig. 1A), which are focal with a necrotic centre surrounded by a granulomatous reaction (Mashaly *et al.*, 1983), have been grouped by Navia *et al.* (1986*b*) into 3 morphological types: (1) necrotizing abscesses consisting of poorly circumscribed areas of necrosis with a variable amount of haemorrhage and including inflammatory cells, lipid-laden macrophages, newly formed vessels and, invariably, tachyzoites and encysted bradyzoites (fig. 1B); (2) organizing abscesses, in which a central area of coagulative necrosis is surrounded by macrophages with organisms present

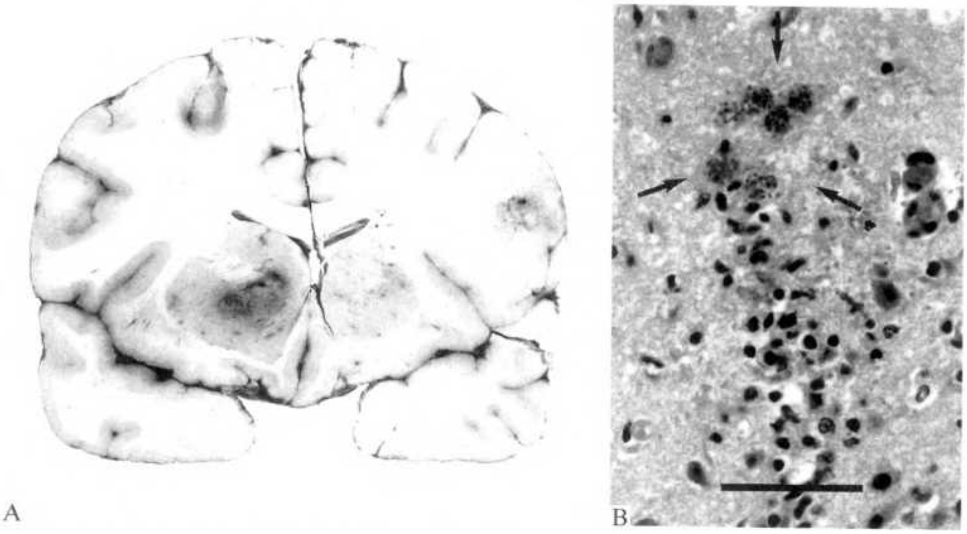


FIG. 1. A, toxoplasmosis. Section of brain showing two areas of necrosis in the right frontal cortex and left deep grey nuclei. The lesions are abscesses in different stages of evolution and contain T gondii trophozoites. B toxoplasmosis. Numerous cysts of T gondii (arrows) are seen in proximity to an aggregate of inflammatory cells. Haematoxylin and eosin. Bar = 50 $\mu$m.

in a minority of cases; (3) chronic abscesses consisting of small and well demarcated cystic spaces containing macrophages and, on rare occasions, organisms. Toxoplasmosis does not represent a diagnostic problem when the organism can be identified or when the presence of coagulative necrosis, resembling an ischaemic area, is strongly suggestive of this parasitosis (Gaston *et al.*, 1985). However, lesions are sometimes atypical diffuse nonnecrotic and pseudoencephalitic, with microglial nodules, astrocytic gliosis and proliferation of microglial cells; in these atypical cases and when the parasite cannot be detected in conventional histological sections, immunohistochemical techniques and electron microscopy have proven of considerable diagnostic value (Conley *et al.*, 1981; Sauron *et al.*, 1983).

A fatal case of meningoencephalitis due to *Acanthamoeba culbertsoni* has been reported recently by Wiley *et al.* (1987). The brain was described as showing severe suppurative meningitis with haemorrhagic necrosis. Trophozoites were found within the necrotic areas and cultured. The morphological features were those of an acute necrotizing rather than a granulomatous process. Another instance of Acanthamoeba infection not involving the brain had previously been reported (Gonzalez *et al.*, 1986).

Infections by other parasites, such as *Pneumocystis carinii* and *Cryptosporidium* (Current *et al.*, 1983) have been described in AIDS patients, but not in the nervous system.

*Mycoses.* The low frequency of mycoses of the nervous system in AIDS patients (Snider *et al.*, 1983; Anders *et al.*, 1986; Hénin *et al.*, 1987) is surprising when compared with their high frequency in other groups of immunocompromized patients in whom toxoplasmosis is a rare occurrence (Hooper *et al.*, 1982).

Cryptococcosis is the least rare type of mycosis in AIDS (Snider *et al.*, 1983; Kovacs *et al.*, 1985); it affected 6% among 2995 patients in New York (Zuger *et al.*, 1986) and was found in 2.6% of the brains by Petito *et al.* (1986). *Cryptococcus* usually produces meningitis or meningoencephalitis and can be identified using India ink staining (Scaravilli, 1984). In the majority of cases the CSF shows pleiocytosis. In 6/7 patients described by Koppel *et al.* (1985), meningitis was the first symptom of AIDS. The meninges may be thickened diffusely or predominantly at the base of the brain and contain a grey-yellow exudate which not uncommonly extends to the ventricles; perivascular spaces may be distended by mucoid material and appear as small cysts. The inflammatory (lymphocytes, plasma cells, eosinophils and multinucleated giant cells, often containing fungi) and/or astrocytic reactions are variable in amount or may be absent.

Candidiasis (Snider *et al.*, 1983; Levy *et al.*, 1984; Koppel *et al.*, 1985), aspergillosis (Britton and Miller, 1984), coccidioidomycosis (Levy *et al.*, 1985*b*) and histoplasmosis (Anders *et al.*, 1986) have each occasionally been observed to cause meningitis, meningoencephalitis, granulomas and abscesses. Nocardiasis has also been reported (Holtz *et al.*, 1985) and in one case, described by Sharer and Kapila (1985), it was associated with Salmonella infection.

*Bacterial infections.* Pyogenic infections are rare (Pitlik *et al.*, 1983). One of the cases described by Moskowitz *et al.* (1984*a*) had *Escherichia coli* menigitis and cerebral microabscesses.

Meningitis, abscesses and tuberculomas, due to *Mycobacterium tuberculosis,* have been occasionally described in Haitians and drug addicts (Fischl *et al.*, 1985; Bishburg *et al.*, 1986). However, another mycobacterium, *M. avium-intracellulare* (MAI) has been frequently reported in AIDS patients (Greene *et al.*, 1982; Zakowski *et al.*, 1982; Elliott *et al.*, 1983; Snider *et al.*, 1983; Sohn *et al.*, 1983; Murray *et al.*, 1984; Anders *et al.*, 1986). In the brains of these patients, MAI is usually present in the cytoplasm of perivascular macrophages and may be associated with lesions due to other causes. MAI is not readily stained with the Ziehl-Neelsen method, but appears in sections stained with PAS (Pappolla and Metha, 1984).

One case of syphilitic involvement of the spinal cord has been mentioned by Berger *et al.* (1984).

*Viral infections. Cytomegalovirus* (CMV) infection was the most frequent neurological complication in the series by Anders *et al.* (1986) and was found in 26% of the brains examined by Petito *et al.* (1986). CMV may produce encephalitis localized to the periventricular region (Hawley *et al.*, 1983; Singh *et al.*, 1986) and has also been considered responsible for many cases of subacute encephalitis. Neuropathological examination of AIDS adults and children suffering from encephalopathy with CT evidence of cerebral atrophy (Snider *et al.*, 1983; Nielsen *et al.*, 1984; Belman *et al.*, 1985; Epstein *et al.*, 1985) showed microglial nodules without neuronophagia and mononuclear infiltration in the grey matter and/or peri-

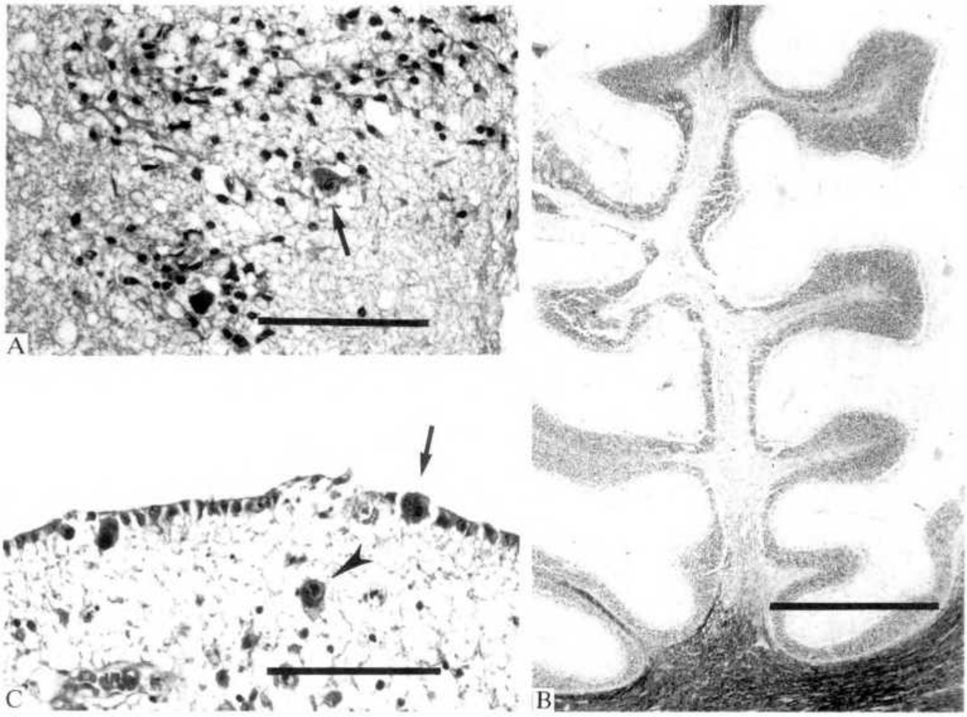


FIG. 2. A, CMV encephalitis. A cortical aggregate of microglial cells includes one cell bearing a CMV intranuclear inclusion (arrow). No lymphocytes and plasma cells are seen. Haematoxylin and eosin. Bar = 100 μm. B, CMV encephalitis. Cerebellar folia showing degeneration of the white matter and relative preservation of the cortical structure. Luxol fast blue/Nissl. Bar = 0.5 mm. C, CMV encephalitis. The nuclei of one ependymal cell (arrow) and of a large astrocyte in the subependymal region (arrowhead) contain CMV inclusions. Haematoxylin and eosin. Bar = 100 μm.

ventricular regions and small areas of demyelination in the white matter. Giant cells containing typical inclusions of CMV could be seen in 6.5% of the microglial nodules (fig. 2A) (Morgello *et al.*, 1987), as well as in areas adjacent to the lesions. The appearances of the grey matter are not those commonly observed in viral encephalitis (Escourolle and Poirier, 1977), but resemble the nodular encephalitis described by Schneck (1965) in patients with immunosuppression, in which CMV could be demonstrated (Dorfman, 1978). The lesions of the white matter (fig. 2B) are also very unusual and no CMV inclusions were found in them; recently, however, Moskowitz *et al.* (1984*b*) showed that CMV could induce white matter lesions in AIDS patients; furthermore, immunocytochemical, ultrastructural and in situ hybridization studies (Morgello *et al.*, 1985; Gray *et al.*, 1987) showed that CMV exists in giant cells as well as in cells of normal appearance and confirmed that the infection predominates in the ependymal and subependymal regions (fig. 2C), from which it spreads into the brain tissue.

*Progressive multifocal leucoencephalopathy* (PML) in AIDS has been described by Miller *et al.* (1982), Bedri *et al.* (1983), Snider *et al.* (1983), Bernick and Gregorios (1984), Katlama *et al.* (1984), and Ho *et al.* (1984), but in all series its incidence is

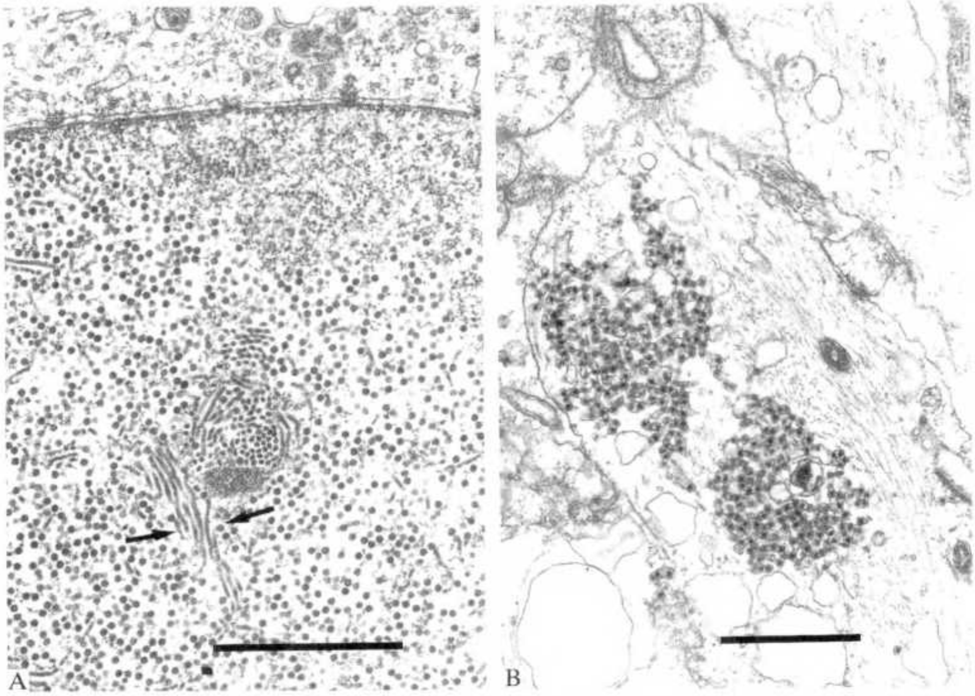


FIG. 3. Progressive multifocal leucoencephalopathy. Electron micrographs show round and elongated (arrows) viral particles inside the nucleus (A). In B, an astrocytic process contains only round particles. Bars = 1 μm.

low; it was present in only 2% of the cases studied by Petito *et al.*, (1986). Pathological features are not different from those previously described by Åström *et al.* (1958) and consist of small confluent areas of demyelination, involving mainly the subcortical and the parieto-occipital regions, containing lipid-laden macrophages, bizarre giant astrocytes and large oligodendrocytes with intranuclear inclusions. The inflammatory reaction is variable in amount, but usually scanty. The virus, which is present within the nuclei (fig. 3A) or in cell processes (fig. 3B), can be visualized by electron microscopic or immunohistological methods.

*Herpes simplex* (HSV) encephalitis (Dix *et al.*, 1985) and myelitis (Britton *et al.*, 1985; Tucker *et al.*, 1985), usually associated with CMV, may occur in AIDS and are due to HSV type II while HSV type I is commonly found in adult cases. Histological diagnosis can be confirmed by ultrastructural and/or immunohistochemical studies.

*Varicella-zoster virus* (VZV) encephalitis has occurred in 3 cases reported by Petito *et al.* (1986) and in 1 by Ryder *et al.* (1986). The lesions are similar to those described by Horten *et al.* (1981) in immunocompromized (other than AIDS) patients and macroscopically consist of multiple and well circumscribed foci of grey-yellow necrosis of the white matter in the brain and spinal cord, similar to those of PML. Histologically the central area of necrosis is surrounded by demyelination but, unlike PML, eosinophilic intranuclear inclusions are present in oligodendrocytes, astrocytes and nerve cells. Immunocytochemical and ultrastructural methods have shown the VZV in the intranuclear inclusions. In addition, Eidelberg *et al.* (1986*a*) have described endarteritis associated with the virus.

### *Cerebral tumours*

*Lymphomas.* These are not uncommon in AIDS and are predominantly extranodal (Di Carlo *et al.*, 1986) and highly malignant. Some of them are true Burkitt lymphomas (Ziegler *et al.*, 1982), neoplasms which are known to be associated with Epstein-Barr virus (EBV) (Andersson *et al.*, 1976), like other cerebral lymphomas in non-AIDS (Hochberg *et al.*, 1983) and AIDS (Rosenberg *et al.*, 1986) patients. The association between EBV and lymphomas is particularly relevant in AIDS patients, all of whom have positive serology for EBV (Fauci *et al.*, 1984). Similarly to the events taking place in Burkitt lymphoma, it can be postulated that, in AIDS patients, multiple clones of B lymphocytes stimulated by EBV and not regulated by T4 lymphomas, may continue to proliferate unchecked. Eventually, one of the clones will predominate; the subsequent proliferation will change from polyclonal to monoclonal as has been observed in other immunosuppressed patients (Hanto *et al.*, 1981).

*Primary lymphomas* of the CNS are the most common extranodal types in AIDS. Morphologically they are angiocentric, like other primary lymphomas of the CNS (Poirier *et al.*, 1985) and consist of large immunoblastic cells. Studies with lymphocytic markers have shown that all are B-cell lymphomas.

Secondary spread from systemic lymphoma or plasmacytomas is less frequent, 2% in the series by Petito *et al.* (1986) compared with 6% occurring as primary tumours. They are usually localized to the subarachnoid spaces, thus making the diagnosis by CSF examination easier than in primary lymphomas. Compression of the spinal cord by epidural masses has also been reported.

*Kaposi sarcoma.* Cerebral deposits of Kaposi sarcoma are rare when compared with the high incidence of this tumour outside the CNS. Although the origin of this condition is debated, it may possibly originate from the endothelial cells of the lymphatic vessels whose absence in the nervous system might explain its rare occurrence. The few observations are probably metastases, since they are always accompanied by foci in the lungs (Gorin *et al.*, 1985).

### *Direct involvement of the CNS by HIV*

Various virological (Ho *et al.*, 1985; Levy *et al.*, 1985*a*; Resnick *et al.*, 1985; Shaw *et al.*, 1985) and immunochemical (Gabuzda *et al.*, 1986) studies have demonstrated the possibility of a direct infection of the nervous system by HIV, resulting in a subacute encephalitis in some patients which would be the anatomical counterpart of the progressive dementia with cerebral atrophy seen in AIDS (Navia *et al.*, 1986*a*).

*Subacute encephalitis.* In an early report by Snider *et al.* (1983), most of the patients with subacute encephalitis had morphological or serological evidence of

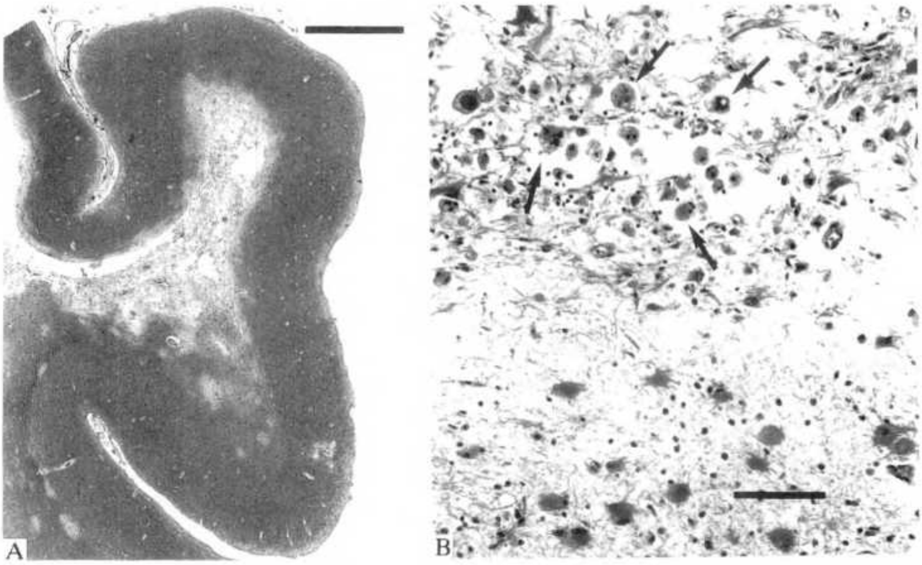


FIG. 4. A, HIV encephalitis producing necrosis and cystic degeneration of the subcortical white matter. Haematoxylin and eosin. Bar = 2 mm. B, HIV encephalitis. An area of degenerated white matter contains large astrocytes (bottom) and multinucleated giant cells (arrows). Haematoxylin and eosin. Bar = 100 μm.

CMV infection. Subsequent virological, clinical and pathological investigations have made it possible to separate from CMV encephalitis (*see* above) a type of subacute process with well defined morphological features. In the series described by Petito *et al.* (1986), this subacute encephalitis, which has been found in 28% of the cases, consists of a predominant involvement of the hemisphere white matter and appears either as diffuse leucoencephalopathy (Kleihues *et al.*, 1985; Gray *et al.*, 1987) with severe loss of myelin which spares the U-fibres or as more circumscribed areas of demyelination which may be necrotic (fig. 4A). Histologically, these areas show loss of axons and contain abnormally large astrocytes and, on occasion, rod cell forms of microglia and mononuclear cells. They are also characterized by the presence of multinucleated giant cells (MGC) (fig. 4B). Microglial nodules in the grey matter are rare; when the leptomeninges are involved, they contain inflammatory cells and, more rarely, MGC.

MGC have been described by Sharer *et al.* (1985) in brains of patients in whom HIV had been demonstrated by hybridization (Shaw *et al.*, 1985) and are considered unique to AIDS by Petito *et al.* (1986). MGC are large, irregularly round, elongated or polyhedral in shape, and also may be localized in the grey matter (Sharer *et al.*, 1985), usually scattered among mononuclear macrophages or in perivascular spaces. Their cytoplasm is eosinophilic and granular and is densely stained in the centre of the cell and vacuolated at the periphery (fig. 5A). The multiple (up to 20) and deeply basophilic nuclei are round or slightly elongated and form a circular or semicircular arrangement at the periphery (fig. 5A) or, less frequently, are clustered at the centre of the cell (fig. 5B) or scattered haphazardly (fig. 5C). MGC

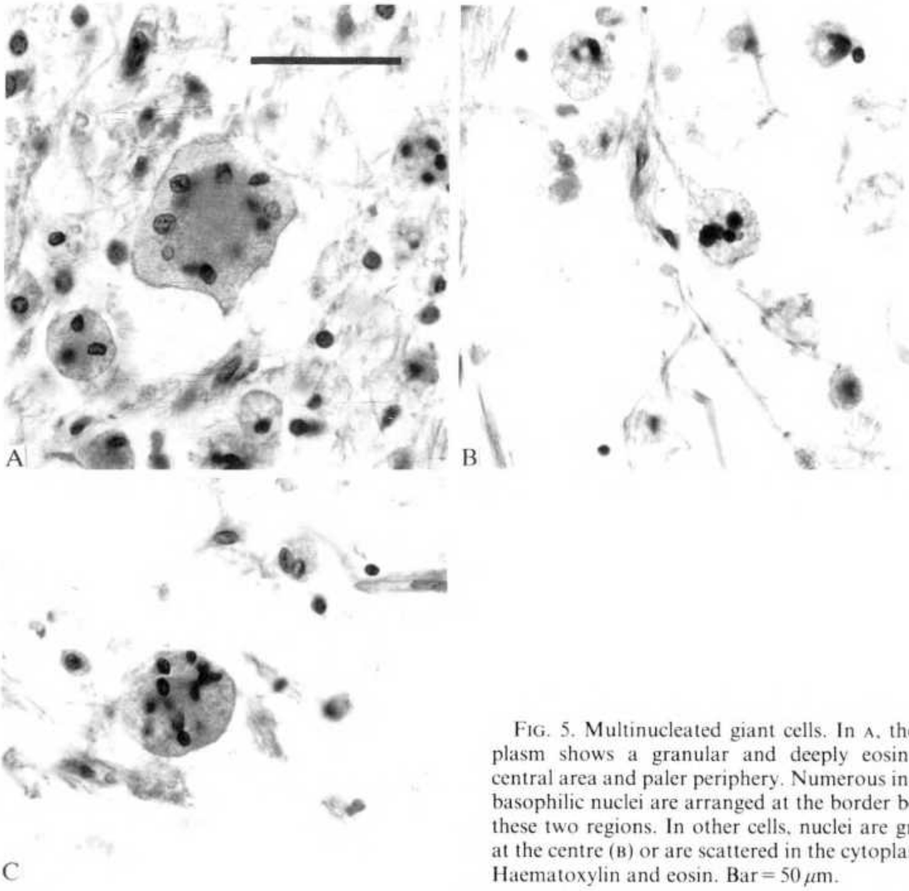


FIG. 5. Multinucleated giant cells. In A, the cytoplasm shows a granular and deeply eosinophilic central area and paler periphery. Numerous intensely basophilic nuclei are arranged at the border between these two regions. In other cells, nuclei are grouped at the centre (B) or are scattered in the cytoplasm (C). Haematoxylin and eosin. Bar = 50 μm.

are diffusely stained with alcian blue and PAS and may contain diastase-resistant, strongly PAS and Sudan-black-positive granular material. Immunohistochemical staining methods using antisera against glial fibrillary acidic protein, S-100, 150 and 200 kDa subunits of neurofilaments, neuron-specific enolase, myelin basic protein, fibronectin, factor VIII, lysozyme and alpha-1-antitrypsin were negative (Budka, 1986). Some giant cells showed a light, diffuse staining for anti-alpha-1-antichymotrypsin and on occasion a distinct cytoplasmic staining for leucocyte common antigen, adjacent to the cell membrane (Budka, 1986). An origin of these cells from lymphocytes has been suggested, since MGC resemble multinucleated cells produced in vitro when cultures of T lymphocytes are exposed to HIV (Popovic *et al.*, 1984). Subsequent immunohistochemical, ultrastructural and in situ hybridization studies have demonstrated their origin from histiocytes (Koenig *et al.*, 1986). In addition, recent investigations suggested that human macrophages can be infected by HIV in vivo and in vitro (Ziza *et al.*, 1985; Salahuddin *et al.*, 1986) and Sharer *et al.* (1986), Mirra *et al.* (1986) and Gray *et al.* (1987) gave

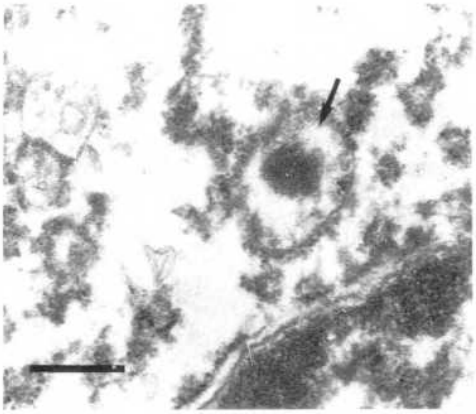


FIG. 6. Electron micrograph of a multinucleated giant cell containing an intracytoplasmic virus-like particle (arrow) close to the nuclear membrane. Bar = 0.5 μm.

ultrastructural evidence of HIV particles in the cytoplasm of MGC (fig. 6). Furthermore, Koenig *et al.* (1986) showed that macrophages and giant cells derived from them represent the main cells capable of synthesizing viral RNA, and thus might be the main reservoir of the virus and the vehicle for spreading the infection. The relationship between histiocytes and HIV may be explained by the finding that these cells contain an epitope (CD4) shared also by T4 lymphocytes (Wood *et al.*, 1983), which is recognized by HIV (Dalgleish *et al.*, 1984). Giant cells, however, are not the only cells in the CNS that contain the virus: immunohistochemical and in situ hybridization studies have shown the presence of virus in endothelial cells and, in a single case, in astrocytes and nerve cells (Wiley *et al.*, 1986). The recent finding that nerve cells also have a differentiation antigen which acts as a receptor for the virus (Pert *et al.*, 1986) leads to interesting implications. One is that these receptors may be targets for virus infection. Indeed, recent results by Shaw *et al.* (cited in Pert *et al.*, 1986) seem to support this view: they found that the amounts of virus recovered from various regions of AIDS brains are similar to the pattern of quantity of receptor. Moreover, the demonstration that a fraction of the HIV envelope, called 'peptide T' is capable of blocking HIV infection of human T cells (Pert *et al.*, 1986), may suggest a possible approach to the treatment of the immunodeficiency syndrome.

In addition to CMV and subacute encephalitis, a third group, termed nonspecific encephalitis, has been described. It includes cases showing scattered microglial nodules but no viral inclusions, organisms or MGC. In these cases the white matter may show pallor and contain some reactive cells.

*Vacuolar myelopathy*. This was described by Goldstick *et al.* (1985), Petito *et al.* (1985) and Singh *et al.* (1986). Petito *et al.* (1986) reported an incidence of 29.6% in their cases. The lesions are symmetric and most severe in the lateral and posterior columns of the thoracic cord and are not always confined to specific anatomical tracts. Ultrastructurally, the vacuoles seen by light microscopy are described by

Petito *et al.* (1985) as intramyelinic swelling with splitting of the lamellae. Axons are normal in mildly affected areas, but are disrupted in areas with severe vacuolation with consequent wallerian degeneration.

These pathological changes resemble those of subacute combined degeneration and suggested that vitamin $B_{12}$ (Pant *et al.*, 1968) or folic acid (Robertson *et al.*, 1971) deficiency might be their cause. However, serum levels of $B_{12}$ and folic acid have been found to be normal (Petito *et al.*, 1985). Furthermore, although vacuolar myelopathy or involvement of the long tracts is occasionally seen in the absence of other pathological changes, its frequent association with the subacute encephalitis and MGC (Horoupian *et al.*, 1984; Kleihues *et al.*, 1985) makes it likely that HIV plays a role in its pathogenesis (Petito *et al.*, 1986), as has been suggested for HLTV I in the tropical spastic paraparesis (Vernant *et al.*, 1986; Montgomery, 1986).

*Mineralization of vessel walls.* Mineralization of the vessel walls of the white matter and the basal ganglia has been described in association with AIDS encephalitis in adults and in children. While a disorder of the metabolism of calcium and phosphorus cannot be excluded, Belman *et al.* (1986) have postulated that mineralization may be due to a direct effect of the HIV on the vessel walls, similar to that seen in congenital rubella.

### *Other lesions*

Vascular lesions which may occur are rarely responsible for the fatal outcome of the disease. Haemorrhages may be found within a tumour or an area of demyelination and are possibly secondary to a defect of coagulation. Ischaemic lesions may be secondary to nonbacterial endocarditis or to diffuse intravascular coagulation. Pontine lesions have been reported by Anders *et al.* (1986), either in the form of central pontine myelinolysis secondary to prolonged hyponatraemia or as focal pontine leucoencephalopathy, similar to that observed in patients who have been given radiotherapy or chemotherapy (Breuer *et al.*, 1978). Wernicke's encephalopathy (Rosemberg *et al.*, 1986), anoxic-ischaemic or hepatic encephalopathy (Petito *et al.*, 1986) may be terminal events.

### *Neuropathological features specific to AIDS*

The neuropathology of AIDS presents specific features not previously seen in other immunocompromized patients. Opportunistic infections are unusual in HIV-positive children, who usually present with a subacute encephalitis with MGC, cerebral atrophy, involvement of the long tracts and calcification of the basal ganglia (Belman *et al.*, 1985; Epstein *et al.*, 1985, 1986). The incidence of the various complications varies from one region to another (Moskowitz *et al.*, 1984*a*; Anders *et al.*, 1986; Petito *et al.*, 1986; Hénin *et al.*, 1987). The frequency of some lesions varies with the evolution of the disease: a retrospective study by Petito *et al.* (1986) has shown that the annual incidence of MGC encephalitis is increasing. This may reflect changes in survival time, viral neurotropism or therapeutic measures and is unlikely to be due to improved accuracy of histological examination.

Whether secondary to the immunosuppression or directly induced by the virus, the morphological appearance of the lesions are often atypical and misleading: in toxoplasmosis, for instance, a pure encephalitic process may be similar to that induced by a virus; in other cases cysts containing the toxoplasma may not be accompanied by any cellular reaction.

AIDS patients may develop pathological lesions due to different agents, either simultaneously or at different stages of the illness and these may appear in one or various organs or even within the same area (Gray *et al.*, 1987); this seems typical of AIDS since it has only rarely been reported in other immunodeficiency syndromes (Hooper *et al.*, 1982): MGC can accompany toxoplasmosis and cryptococcosis (fig. 7); furthermore, cases have been reported which include white matter lesions, MGC and intranuclear inclusions characteristic of CMV (fig. 8) and/or papova (fig. 9) virus (Kleihues *et al.*, 1985; Gray *et al.*, 1987). The coexistence of these lesions may be at the root of different interpretations of the aetiology of the subacute encephalitis in AIDS (Morgello *et al.*, 1985; Anders *et al.*, 1986; Fénelon *et al.*, 1986; Petito *et al.*, 1986) and has led Kleihues *et al.* (1985) to discuss the possibility of a combined action of HIV and/or one or several other virus (CMV, papova virus) to produce the leukoencephalopathy.

### *Use of brain biopsy*

The variety of pathological findings associated with AIDS raises the problem of the importance and value of diagnostic brain biopsy. The use of stereotactic methods has certainly made this approach safe and accurate. Furthermore, the possibility that AIDS patients may develop cerebral diseases unrelated to HIV and amenable to treatment should be considered. On the other hand, the evidence that multiple agents are sometimes present in different areas of the brain, the often atypical morphological features and the inefficacy at present of any treatment should discourage the indiscriminate use of brain biopsy in AIDS patients.

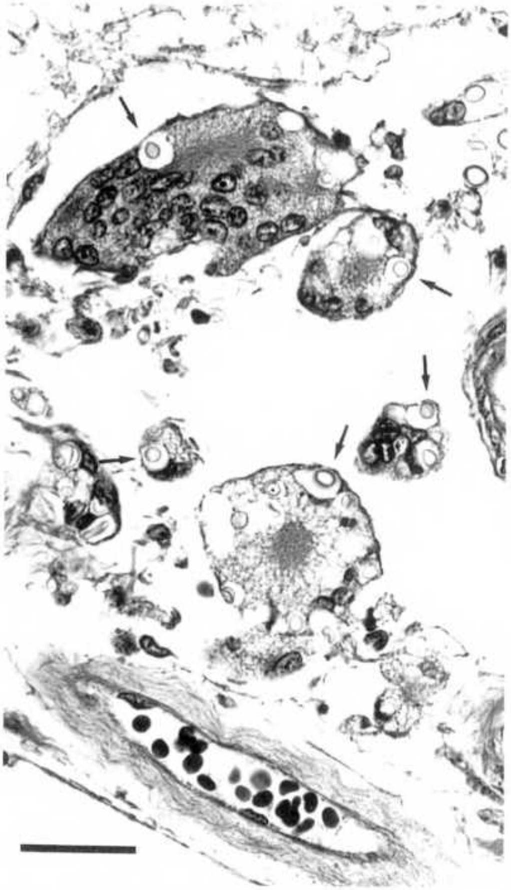
## *Involvement of the peripheral nervous system and muscles*

This may occur at any stage of the disease (Dalakas and Pezeshkpour, 1986). The description of the pathological changes is based mainly upon biopsy material which has shown nonspecific lesions, but more data have been obtained from a few postmortem studies.

### *Peripheral neuropathy*

Peripheral neuropathy may develop in patients with AIDS (Snider *et al.*, 1983) or with AIDS-related complex (ARC) (Lipkin *et al.*, 1985; Leport *et al.*, 1987) or may represent the sole clinical sign of HIV seroconversion (Piette *et al.*, 1986; Cornblath *et al.*, 1987).

*Painful sensory neuropathy.* This syndrome was first described in AIDS by Snider



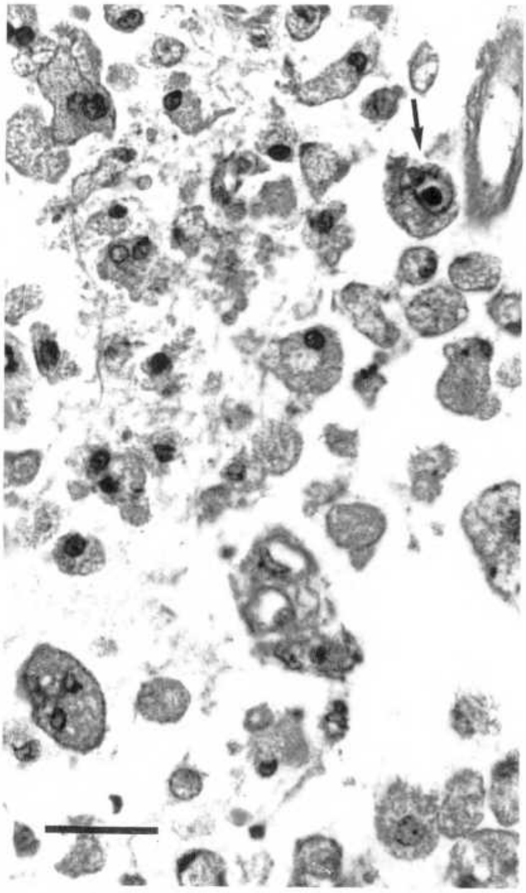


FIG. 7. (*left*). A granulomatous area in the leptomeninges contains several giant cells. One of them (top) is of Langhans type; the others are of the type associated with HIV encephalitis. Both types contain cryptococci (arrows). Haematoxylin and eosin. Bar = 40 $\mu$m.

FIG. 8. (*right*). An area of degeneration in the periventricular region contains an aggregate of macrophages and one multinucleated giant cell (bottom left). The nucleus of one cell (arrow) contains an inclusion of cytomegalovirus. Haematoxylin and eosin. Bar = 40 $\mu$m.

*et al.* (1983) and has subsequently been observed in the preterminal phases of the disease by Simpson *et al.* (1985) and Cornblath *et al.* (1987). The neuropathy involves predominantly small myelinated and unmyelinated fibres (Simpson *et al.*, 1985) and is thought to be a distal axonopathy in which nutritional and toxic factors may be implicated (Snider *et al.*, 1983). Alternatively, it could reflect infection of sensory ganglia by HIV (Cornblath *et al.*, 1987). On one occasion CMV was found in the Schwann cells of unmyelinated fibres in the nerves supplying the adrenal gland (Dalakas and Pezenshkpour, 1986).

*Inflammatory demyelinating peripheral neuropathy* (*IDP*). This was first described in AIDS by Horowitz *et al.* (1982) and seems to occur with high frequency among individuals at risk for HIV infection (Cornblath *et al.*, 1987). It is identical in presentation and course either to the Guillain-Barré syndrome or to chronic

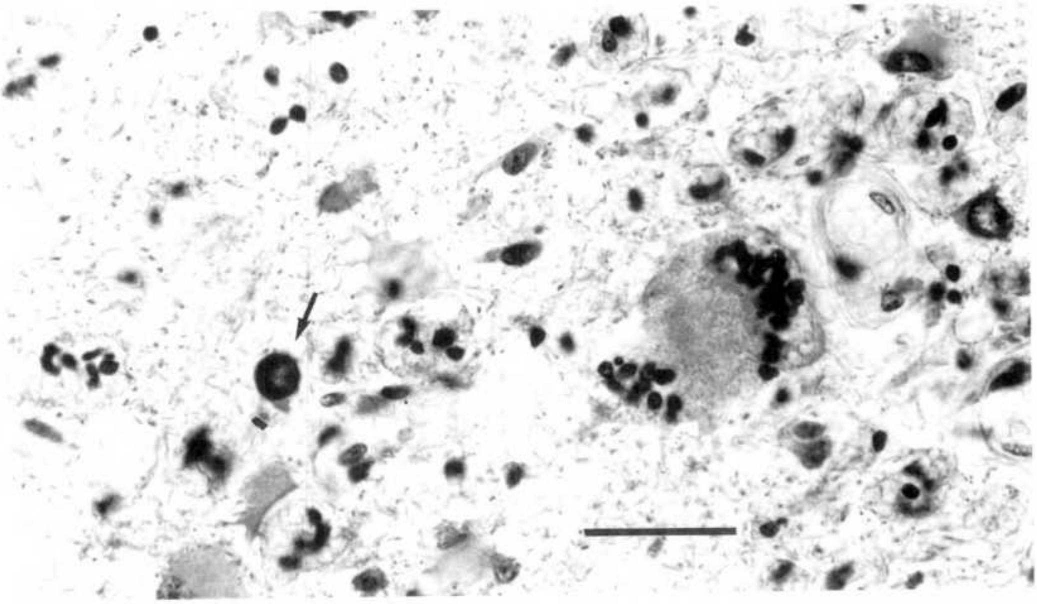


FIG. 9. Subcortical white matter in a case of PML showing large astrocytes and one oligodendrocyte. The nucleus of the latter (arrow) contains a basophilic inclusion. In addition, one MGC is also present, in which nuclei form an aggregate at one pole of the cell body. Haematoxylin and eosin. Bar = 50 $\mu$m.

inflammatory demyelinating polyneuropathy, except for the presence of pleiocytosis of the CSF (Cornblath *et al.*, 1987; Leport *et al.*, 1987). In most cases, nerve biopsy shows perivascular inflammatory infiltrates in the epineurium, perineurium and endoneurium (Cornblath *et al.* 1987; Leport *et al.*, 1987) consisting of T8 lymphocytes (Leport *et al.*, 1987). Similar cuffings are occasionally seen in muscles. The inflammatory response varies considerably and seems most severe when IDP is associated with ARC or HIV seroconversion (Leport *et al.*, 1987). Nerve abnormalities include axonal degeneration and/or segmental demyelination (Dehen *et al.*, 1985; Cornblath *et al.*, 1987; Leport *et al.*, 1987).

HIV has been isolated from the CSF and sural nerve in 1 patient with IDP (Ho *et al.*, 1985) and intrathecal production of HIV-specific IgG was demonstrated in 3 out of 4 cases of Leport *et al.* (1987). However, in situ hybridization performed on nerve biopsies of 4 patients with IDP failed to demonstrate the HIV genome in Schwann cells, lymphocytes or perineurial cells (Cornblath *et al.*, 1987). These authors think it unlikely that retrovirus infection is the primary mechanism causing IDP and suggest that it may derive from an altered immune regulation produced by the HIV infection.

The role of CMV in the pathogenesis of IDP, already suspected for a long time in cases of Guillain-Barré syndrome, has been strongly supported by the observation in postmortem material of CMV inclusions in the peripheral nervous system of AIDS patients (Moskowitz *et al.*, 1984*b*). These findings were subsequently confirmed by Bishopric *et al.* (1985) and Dalakas and Pezeshkpour (1986) in the Guillain-Barré syndrome and by Eidelberg *et al.* (1986*b*) in progressive polyradiculopathy associated with AIDS . The inclusions were observed in spinal roots, cauda equina and proximal nerve segments, but not in spinal ganglia, distal nerves and muscles. They were located mostly in Schwann cells, but also in enlarged endoneurial cells. Associated pathological features included acute and subacute inflammatory infiltrates, demyelination and focal necrosis of nerve fibres. In addition, Eidelberg *et al.* (1986*b*) described focal vasculitis with thrombosis in the spinal roots. They also observed CMV inclusions in the CNS, located in ependymal cells and subependymal astrocytes and suggested that CMV infection of the periventricular brain tissue spread through the CSF and that hydrostatic pressure explained the severity of the lesions at the lumbar level. It is uncertain whether CMV represents a direct cause of neuropathy or only triggers an immunopathogenetic process responsible for the IDP.

'*Mononeuritis multiplex*'. A multifocal neuropathy, sometimes involving cranial nerves, with spontaneous remission or evolving into a distal symmetric polyneuropathy, is the commonest neuropathy (9/12) in the series of Lipkin *et al.* (1985). CSF abnormalities, including pleocytosis, were present in all patients. Sural nerve biopsy, which was performed in 4 patients, was normal in 1 case, showed axonal degeneration and demyelination in 2 cases and axonal degeneration in 1. In these 3 latter cases epineurial and endoneurial perivascular mononuclear inflammatory cells were present but there was no vasculitis. Similar clinicopathological features have been reported by Dalakas and Pezeshkpour (1986) and Leport *et al.* (1987). Necrotizing vasculitis in the peripheral nerves has seldom been recorded (Dalakas and Pezeshkpour, 1986; Cornblath *et al.*, 1987).

*Other conditions*. Lymphomatous infiltration of the cranial and/or peripheral nerves has been observed in 5/88 homosexual patients suffering from non-Hodgkin lymphomas (Ziegler *et al.*, 1984). Other types of PNS involvement have occasionally been reported in patients with HIV infections such as rapidly progressive amyotrophic lateral sclerosis (Hoffman *et al.*, 1985) or subacute sensory noninflammatory demyelinating neuropathy involving fibres larger than 8 μm (Dalakas and Pezeshkpour, 1986).

### *Myopathy*

Muscle diseases are less frequently observed in patients infected by HIV.

*Polymyositis*. This can precede the appearance of ARC or AIDS (Dalakas and Pezeshkpour, 1986). HIV antigens have been detected by immunofluorescence in the inflammatory cells, but not in muscle fibres. These cases show striking similarities with polymyositis described in 50% of monkeys with simian AIDS due to a simian (SRV-1) retrovirus (Dalakas *et al.*, 1986).

*Nonspecific changes*. Nonspecific type II fibre atrophy associated with proximal muscle weakness is presumably due to poor nutrition, rapid weight loss or as a remote effect of lymphomas (Dalakas and Pezeshkpour, 1986).

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# ORIENTING OF VISUAL ATTENTION IN PROGRESSIVE SUPRANUCLEAR PALSY

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## SUMMARY

Orienting of visual attention was studied in 8 patients with progressive supranuclear palsy (PSP) and 8 parkinsonian control subjects. While maintaining fixation on the centre of a visual display, subjects made simple reaction time (RT) key press responses on detecting visual targets which appeared above, below, to the left or right, equidistant from fixation. On each trial the target was preceded by a preparatory cue, either a peripheral luminance change or a central arrow, to summon attention to one of the four locations. The orienting of attention was measured as a facilitation in detection RT at the cued location. For the parkinsonian controls, this facilitation was equal for horizontal and vertical directions, whereas for both types of cues, PSP patients were slower moving attention in the vertical than in the horizontal plane Midbrain retinotectal pathways are important not only for controlling eye movements, but also for orienting attention.

## INTRODUCTION

In everyday life, the orienting of attention to a point of interest is usually accompanied by overt movements of the head, eyes or body. This is so whether attention is summoned exogenously by a sensory signal, as in turning towards a movement seen out of the corner of the eye, or deployed endogenously, as when we decide to look both ways before crossing the street. Contemporary research has shown, however, that neural mechanisms exist for covertly orienting attention which are distinct from those controlling eye movements (Posner, 1980; Posner *et al.*, 1982). These align internal attention with a spatial position to facilitate processing of signals from it, while inhibiting the processing of other signals in the visual field. Attention may be shifted even when the eyes remain fixed; and under certain circumstances, attention may move in one direction while the eyes move in another (Posner, 1980).

With progress in our understanding of the neurobiology of attention, the concept

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of a distributed network (Mesulam, 1981) has emerged in which cortical and subcortical centres are coordinated in governing the allocation of visual attention, and in integrating attention systems with oculomotor control. The current communication focuses on the contribution of the subcortical midbrain systems to the orienting of visual attention. The encephalization of visual function in the cortex is a relatively recent development in phylogeny; the geniculostriate pathways are well developed only in mammals. In nonmammalian vertebrates, the superior colliculus of the midbrain serves as the primary visual centre both for visual perception and for the deployment of visual attention. This phylogenetically older retinotectal pathway persists in mammals, and a retinotopic map of the visual field is represented in the superior colliculus. Since the colliculus is intimately connected with oculomotor systems, neurophysiologists have been especially active in studying its role in perceptuomotor integration of attention and eye movement (Wurtz and Albano, 1980). Yet clinical neurology and neuropsychology have shown less interest in the role of the colliculus in regulating visual attention. Since focal lesions of the dorsal midbrain cause such dramatic deficits in consciousness, eye movements, motor and sensory function, coexisting deficits in selective visual attention are generally overshadowed, and usually contribute little to diagnosis and clinical localization.

In progressive supranuclear palsy (PSP), abnormalities of orienting behaviour are a salient component of the clinical picture. This degenerative disorder affects subcortical nuclei of the basal ganglia and brainstem. It shares many of the signs of Parkinson's disease, but is distinguished from it by several pathological and clinical differences (Steele *et al.,* 1964). Most important among these is supranuclear ophthalmoplegia, affecting vertical more than horizontal gaze, which is associated with a unique degeneration of the superior colliculus and peritectal region. While the ophthalmoplegia is pathognomonic and an essential requirement for making the diagnosis, it is but one component of a more global derangement of visually guided behaviour. Rafal and Grimm (1981) emphasized deficits in spatial orienting which were not caused, directly, by impaired ocular motility. We observed that even when our patients were still able to move their eyes, they seemed disinclined to do so, and behaved as though blind. These patients often fail to turn towards those who approach them, to maintain eye contact during conversation, or to look at their plates when eating, even though they may still be able to do so on command. The study of PSP patients thus affords a special opportunity to examine the role of the phylogenetrically older 'second visual system' (Schneider, 1969) of the midbrain in man.

In the current investigation, we studied covert orienting of visual attention in PSP using an experimental approach developed by Posner (1980) for measuring shifts of visual attention not dependent on eye movements. This paradigm is first described, and the results of a preliminary study in PSP patients (Posner *et al.*, 1982) are summarized to introduce the current investigation.

## METHODS AND SUBJECTS

### *Experimental paradigm*

Fig. 1 shows the experiment used by Posner *et al.*, (1982) to study normal subjects. The task was to detect a target which appeared with equal probability in either of two boxes, and to respond with a simple reaction time (RT) manual key press. On each trial the target was preceded by a preparatory cue which was the brief brightening of one of the flanking boxes. In this experiment the cue was *valid*, i.e., the target subsequently appeared at the location primed by the cue, on 80% of the trials; in 20% of trials the cue was *invalid*, and the target subsequently appeared in the contralateral box. The results were quicker detection RTs on valid cue trials, when attention had been oriented to the correct location for detecting the target, compared with invalid cue trials. Since the motor response was the same regardless of the type of cue, and since no eye movements occurred, the facilitation of detection by a valid cue was attributed to an internal shift of covert attention towards the cue. As shown in fig. 1, the time interval between cue and target was varied so that the speed of orienting could be measured as a build up in the effect of cue validity over time. An effect of attention orienting was evident with cue-target intervals as short as 50 ms in these normal subjects.

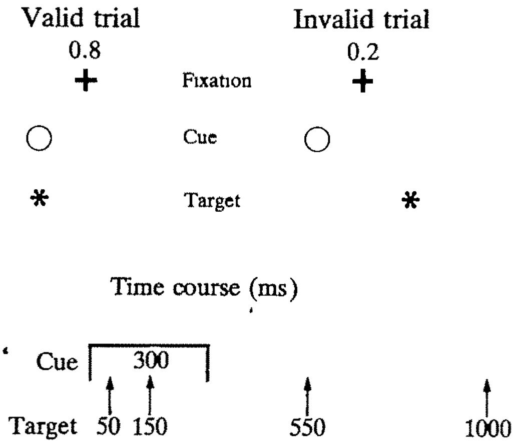


FIG 1. Experimental paradigm used by Posner *et al.* (1982) for measuring covert shifts of visual attention. Subjects fixated the centre of the screen and made a simple reaction time (RT) key press on detecting a target which appeared with equal probability within either of the two peripheral circles. Each trial began with a cue to summon attention to one of these locations In this particular experiment, the cue was a peripheral luminance change which also predicted the probable location of the forthcoming target; thus exogenous and endogenous contributions of the cue were redundant The speed of shifting covert attention was measured as a *difference* in detection RT for valid and invalid cues as a function of cue-target interval In the current investigation, attention shifts in the horizontal plane were compared with those in the vertical plane, and two different cuing conditions were tested *exogenous cuing* in which attention was summoned by a peripheral luminance change which did not predict the location of the forthcoming target; and *endogenous cuing* in which attention was directed by a central arrow which predicted the location of the forthcoming target with an 80% probability.

Posner *et al.* (1982) reported preliminary findings in this experiment in 4 PSP patients. In that experiment there were four target positions equidistant from fixation: left, right, above and below. The orienting of attention was shown to occur with a longer latency in the vertical than in the horizontal plane. Thus an effect of cue validity was present in the horizontal plane at a cue-target interval of 50 ms, whereas, in the vertical plane, no effect of attention orienting was present until the longest cue-target interval (1000 ms). The small number of subjects in that experiment did not, however, permit us to determine whether the smaller orienting effect in the vertical plane was due to relatively slower detection on valid trials, or to quicker detection on invalid trials, in the vertical plane. Moreover, the results did not allow us to determine whether the midbrain is involved, selectively, in orienting to exogenous visual signals, under endogenous control, or both. In that experiment the cue had been a sensory signal at one of the possible target locations which could reflexly summon attention to it; but the cue also predicted the likely target location, permitting subjects to shift their attention based on a strategic set. In that experiment, therefore, the exogenous and endogenous contributions of the cue for orienting attention were redundant.

Posner *et al.* (1982) also showed that exogenous and endogenous orienting were separable in normal human subjects. In that experiment, the cue was the brightening of a peripheral box which predicted, with 80% probability, that the target would appear at the location *contralateral* to the cue. The results were quicker detection RTs at the location of the cue at early cue-target intervals; whereas for targets appearing more than 200 ms following cue onset, RTs were quicker for targets contralateral to the cue, i.e. where the subject had *expected* the target. This result suggested that attention is summoned automatically by exogenous sensory signals, but that it may also be deployed endogenously based on a strategic set. The experiment in the PSP patients did not distinguish between these two mechanisms for orienting attention.

The current experiment was undertaken to specify whether midbrain visual centres are involved in exogenous orienting, endogenous orienting or both. We speculated that the more primitive midbrain system might be necessary only for reflexive orienting to exogenous signals, and that endogenous orienting, which presumably requires cortical processing, might proceed normally in the presence of peritectal lesions. Accordingly, we measured attention shifts activated by two different types of cues. In the *exogenous* cuing condition, the cue was the brightening of a peripheral box which did not predict (50% probability) the location of the subsequent target. Since the cue did not indicate to the subjects where to expect the target, any effect of the cue on detection RT could, therefore, be attributed to automatic, stimulus driven orienting. In the *endogenous* cuing condition, an arrow appeared at the centre of the screen which pointed left, right, up or down, and which predicted (with 80% probability) the location of the subsequent target. Since this arrow cue did not involve a luminance change at any of the possible target locations, and therefore cued a peripheral location only by inducing an expectation through its symbolic meaning, any effect it had on detection RT could be attributed to endogenously controlled orienting.

For both types of cues, orienting in the vertical plane was compared with orienting in the horizontal plane in 8 PSP patients and 8 control subjects with Parkinson's disease. Rafal *et al.* (1984) previously studied covert orienting of attention in parkinsonian patients, tested both on L-DOPA/carbidopa, and when they were more bradykinetic off medication, and showed that symptoms of dopaminergic deficiency were not accompanied by any impairment in shifting visual attention. However, only horizontal attention movements were examined. Therefore, in the current experiment, both vertical and horizontal attention shifts were studied in the parkinsonian controls. In this way, any selective deficits in vertical orienting which might be found in PSP patients, but not parkinsonians, could be attributed to the peritectal lesions rather than to other lesions of the basal ganglia which are present in both PSP and in Parkinson's disease.

### *Subjects*

The subjects in this experiment included 8 patients with PSP, and 8 control subjects with idiopathic Parkinson's disease. The PSP patients included 2 men and 6 women with a mean age of 74.6 yrs. Table 1 summarizes the clinical findings in these patients. In the Table a rating of + + + + indicates the most severe impairment. Rating scales for overall disability, social orienting and orienting to the lower visual field are based on those of Rafal and Grimm (1981); rating for the relative severity of ophthalmoparesis for horizontal and vertical eye movements are based on Posner *et al.* (1985). The parkinsonian subjects included 6 men and 2 women ranging in age from 48–85 yrs (mean 66 yrs).

### *Apparatus and procedures*

In a quiet darkened room, subjects faced a black and white TV monitor placed 37 cm in front of them at eye level. The index finger of the preferred hand rested on a single response key placed on a table between the subject and the TV monitor. The TV monitor and response board were interfaced with a microcomputer which controlled the stimulus display and the recording of RT. Light pressure on the response key activated a microswitch to record RT on line.

TABLE 1. CLINICAL DATA

| | | | *Ophthalmoparesis* | | *Orienting* | | | |
|---|---|---|---|---|---|---|---|---|
| *Patient* | *Age/Sex* | *Disability** | *Horizontal* | *Vertical* | *Social* | *Low fld* | *Dementia* | *Meds* |
| M A. | 72/F | + | + | + + + | + | + | N | T,B |
| C.V | 76/F | + + + + | + + | + + + | + + | + + | + + | – – – |
| M S. | 76/F | + + + + | + + + | + + + + | + + + | + + + + | + + | S,M |
| M.L | 65/F | + | + | + + + | + | + | + | S,P |
| S R. | 74/M | + + + + | + | + + | + + | + + | + + | S |
| M F | 80/F | + + + | N | + | N | + | + | P |
| P S | 80/F | + + + | + + | + + + | + | + + | + | S,A |
| F F. | 74/M | + + + + | + + | + + + + | + + + | + + + | + + | S |

*Disability ratings follow Rafal and Grimm (1981) and Posner *et al.* (1985) (*see* text) N = normal Meds S = L-DOPA-carbidopa, B = bromocriptine, M = methysergide, P = procyclidine, A = amantadine; T = trihexphenidyl, Low fld = to orienting toward the lower visual field

Subjects fixed on a central + sign which was flanked by four unfilled, square boxes, 1° across, which were plotted 10° of visual angle above, below, to the right and to the left of fixation. Subjects were instructed to maintain fixation at the central plus sign, and to respond with a quick manual keypress response whenever a target appeared in any of the boxes. Eye position was monitored with closed circuit video, or by direct observation, to ensure that subjects understood the directions, and did not move their eyes. The target was a large bright asterisk filling the box, and each of the four boxes was equally likely to contain the target on each trial However, 50, 150, 350, or 550 ms before the onset of the target, a cue was presented to summon attention. These four cue-target intervals occurred with equal probability, and were varied randomly within blocks of trials.

Two types of cues were tested in separate blocks. In the *exogenous* cuing condition, the precue consisted of the brightening of one of the peripheral boxes for 300 ms. This cue did not predict the location of the forthcoming target; on each trial the target was equally likely to occur at the location of the cue, or opposite to this position. In the *endogenous* cuing condition, a central arrow, 1° of visual angle in length, was used to signal the likely position of target occurrence; e.g., the subsequent target occurred at the location cued by the arrow with an 80% probability, and at the opposite location with a 20% probability. For both cue conditions, cues and targets were always in the same plane, i.e., horizontal or vertical. No information was given to subjects concerning the predictive significance of the cues. For both box and arrow cue blocks they were simply told that when the cue appeared (box or arrow) they were to 'get ready', but 'don't press the button until you see the star' (i.e. target).

Before collecting data on each block, subjects were given practice to ensure that they complied with the instructions: that is, to respond only to targets, not cues; and to keep the eyes fixed in the centre. Once the subjects understood the instructions, they all kept the eyes fixed in the centre of the display, and no anticipatory eye movement responses were made by either group during blocks in which data was collected.

In these experiments the target was a large bright signal, easily visible 10° from the centre, not in the far periphery. The making of an eye movement in response to the cue does not make the task easier for the subjects. On the contrary, it slows performance on the reaction time task (Posner and Cohen, 1980), making it more effortful. The most efficient and natural way to perform this task is to keep the eyes centred; subjects will, in fact, adopt this strategy even if no specific eye movement instructions are given. In experiments with young volunteers, anticipatory eye movement errors seldom exceed 4%. In older subjects eye movement errors are negligible.

Each trial began, after an intertrial interval of 1500 ms, with the offset of the central + sign following, 500 ms later, by the onset of the cue. Blocks consisted of 160 trials. There were two blocks with exogenous cuing and four blocks of endogenous cuing, and the order of the two cue types was randomized within subjects. Oral and written informed consent was obtained from all subjects.

## RESULTS

Trials in which target detection RTs were less than 150 or longer than 3500 ms were excluded from analysis. This resulted in exclusion of less than 4% of trials for the parkinsonian controls, and less than 7% of trials for the PSP patients. The greater number of errors in the PSP group was due to the performance of the 2 subjects with some dementia symptoms. These 2 subjects made both more anticipatory errors (responding to cues instead of waiting for targets), and had more trials in which they failed to respond. The errors made for vertical and for horizontal trials were not different in either subject group.

Median RTs from the remaining trials for each subject, in each condition were calculated and were subjected to a repeated measures analysis of variance (ANOVA). There was one between factor, group (PSP or parkinsonian), and four within factors: type of cue (peripheral box or central arrow); direction (vertical or horizontal), cue validity (valid cue or invalid cue); and cue-target interval (stimulus onset asynchrony of 50, 150, 350 or 550 ms).

Mean RT was slower for the PSP patients (871 ms) than for the parkinsonian control subjects (523 ms), (F $(1,14)=9.8$, $p<0.01$). There was no main effect of target position (vertical vs horizontal) for either group. For both groups RTs were quicker at the longer cue-target intervals (F $(3,42)=19.1$, $P<0.001$). For both groups RTs in the central arrow cue condition were slower at the early cue-target intervals than for the peripheral box cue condition (F $(3,42)=8.8$, $P<0.001$). This difference was greater in the PSP patients (F $(3,42)=3.1$, $P<0.05$), and resulted in significant group × cue (F $(1,14)=1.3$, $P<0.05$), and group × interval (F $(3,42)=4.9$, $P=0.005$) interactions. This difference, however, did not interact with direction of attention shifts.

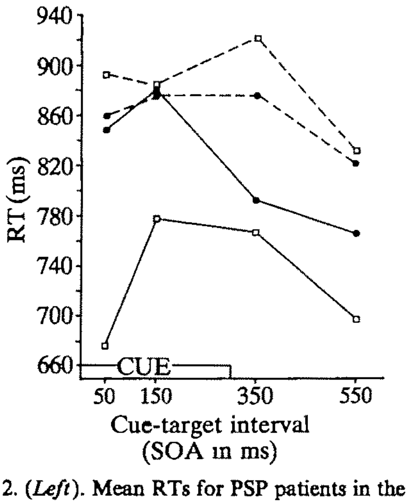
TABLE 2 MEAN RT IN MS FOR PSP PATIENTS AND PARKINSONIAN CONTROL SUBJECTS FOR HORIZONTAL AND VERTICAL TARGETS IN VALID AND INVALID CUE CONDITIONS

| | *PSP* | | | *Parkinsonian* | | |
|---|---|---|---|---|---|---|
| | *Valid* | *Invalid* | *Diff* | *Valid* | *Invalid* | *Diff* |
| Horizontal | 787 | 928 | 141 | 489 | 557 | 68 |
| Vertical | 863 | 908 | 45 | 490 | 558 | 68 |
| Difference | | | 96* | | | 0 |

* $P \pm 0\ 025$.

The purpose of the experiment was to measure the orienting of attention, and the important results, therefore, related to the effects of cue validity. For both subject groups, for both types of cues (arrow and box), RTs were quicker for the valid cue condition (F (1,14)=73.9, $P<0.001$). Thus both exogenous and endogenous cuing were effective in summoning attention. The main result of the experiment was that the effect of cue validity (i.e., RT for invalid trials minus RT for valid trials) was smaller in the vertical plane than in the horizontal plane for the PSP patients, but not for the parkinsonian controls (F (1,14)=6.6, $P<0.025$) (Table 2). This difference in orienting in vertical compared to horizontal directions between the two groups was larger for exogenous (box) than for endogenous (arrow) cuing conditions, but this group × cue type × direction × validity interaction did not achieve significance (F (1,14)=1.5, $P$=n.s.). Separate ANOVAs for box and arrow cue conditions comparing PSP and parkinsonian controls revealed that the impairment in vertical orienting for PSP patients was marginally significant for box cues (F (1,14)=4.4, $P=0.52$), but not for arrow cues (F (1,14)=1.5, $P$=n.s.).

Fig. 2 shows the data for the PSP patients for box cues, and fig. 3 their data for arrow cues. The effect of cue validity on detection RT is shown for horizontal and vertical attention movements as a function of cue-target interval. These figures emphasize the main result of the experiment: a smaller effect of cue validity was present in the vertical plane for both types of cues (box and arrow) at all cue-target intervals. A separate ANOVA for the data from the PSP patients alone confirmed a significant interaction between cue validity and direction (F (1,7)=7.3, $P<0.05$). Further post hoc ANOVAs for the PSP data analysing box cue and arrow cue



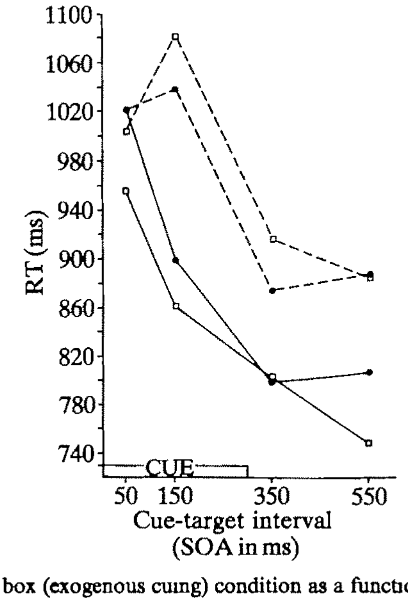


FIG. 2. (*Left*). Mean RTs for PSP patients in the peripheral box (exogenous cuing) condition as a function of cue-target interval. Horizontal = open squares; vertical = closed circles. Valid cue = solid lines; invalid cue = dashed lines. SOA = stimulus onset asynchrony.

FIG. 3. (*Right*). Mean RTs for PSP patients in the central arrow (endogenous cuing) condition as a function of cue-target interval. Horizontal = open squares; vertical = closed circles Valid cue = solid lines, invalid cue = dashed lines. SOA = stimulus onset asynchrony.

conditions independently revealed that, although neither alone achieved statistical significance, a trend toward significance was present for each: box cue (F (1,7) = 3.8, $P < 0.09$); arrow cue (F (1,7) = 4.7, $P = 0.07$).

Inspection of the figures reveals a number of other interesting aspects of the data. The smaller validity effect in the vertical direction is due chiefly to the slower detection RTs in the vertical plane for valid trials. Although there is also a tendency for quicker vertical detection RTs for invalid trials to contribute to the effect, ANOVAs examining only invalid trials did not reveal this interaction to be significant for the PSP group (F (1,7) = 0.66) or when the PSP patients were compared with parkinsonian controls (F (1,14) = 0.56).

Inspection of the figure also appears to indicate that, for both types of cues, the latency of attention movements is longer in the vertical plane. Whereas, in the horizontal plane, an effect of cue validity is present at the 50 ms cue-target interval for both box and arrow cues, there is no evidence of attention shifts (i.e., no validity effect) in the vertical plane until the 150 ms interval for arrow cues, and until the 350 ms interval for box cues. However, an ANOVA for the data from the PSP subjects failed to reveal a significant interaction between validity, direction and interval (F (3,21) = 0.39).

Inspection of the data in fig. 2 also appears to suggest that the impairment in shifting attention vertically may be more severe in the exogenous cuing (box) condition, than in the endogenous cuing (arrow) condition. The difference in the size of the validity effect in vertical as compared with horizontal directions is greater in the exogenous cuing (115 ms) than in the endogenous cuing (57 ms) condition. Moreover, the latency for the attention shift in the vertical direction appears, as mentioned above, to be longer in the exogenous than in the endogenous cuing condition. As noted above, however, when compared with the parkinsonian controls this interaction with cue type did not achieve statistical significance. It is possible that the failure to identify statistical significance for this interaction derived from the fact the data from the invalid cues, in the PSP patients, were so similar in vertical and horizontal directions. We therefore performed a post hoc ANOVA for the valid cue trials only, comparing PSP and parkinsonian groups. This analysis did reveal a significant group × cue type × direction interaction (F (1,14) = 4.7, $P < 0.05$). A conservative interpretation of these results is that PSP subjects are impaired in orienting attention in the vertical plane in response to both exogenous signals and under endogenous control, but that this impairment may be relatively more severe for exogenous than for endogenous orienting.

## DISCUSSION

The phylogenetically older retinotectal pathway is closely related, anatomically, to midbrain oculomotor centres, and lesions in these pretectal centres account for the striking ophthalmoplegia of PSP. The clinical deficits in orienting behaviour in these patients (Rafal and Grimm 1981) suggest that the midbrain also plays an important role in regulating visual attention in man. The results of the current investigation confirm, experimentally, that PSP patients are impaired in the covert orienting of visual attention in the vertical plane.

In this study the covert orienting of visual attention was measured in terms of the size of the validity effect which preparatory cues had on detection RT. The major result of the experiment was that this validity effect was smaller in the vertical plane for PSP patients. Indeed, the validity effect in the vertical plane was systematically smaller in these patients at all cue-target intervals in both exogenous (box) and endogenous (arrow) cuing conditions. It is important to note that the defect in vertical orienting was present even at cue-target intervals as short as 50 ms. This interval is much shorter than the latency for saccades even in normal individuals. Therefore, even if our subjects had made saccades which our monitoring system could not detect, eye movements cannot have been the cause for this result. We can conclude, therefore, that PSP patients have a defect in orienting covert attention in the vertical plane and that this defect is independent from the disorder of ocular motility. Further consideration of the pattern of these results in the PSP patients may permit us to specify more precisely the role that midbrain structures play in orienting visual attention, especially when these findings are contrasted with those obtained in other patients with attention deficits.

### *The defect in covert orienting in PSP*

Inspection of figs 2 and 3 reveals that the smaller validity effect in the vertical plane is due chiefly to slower RTs in the valid cue condition. Although detection RTs in the vertical plane were also generally quicker in the invalid cue condition, this difference was much less pronounced, and was not significant. The validity effect as reflects both the 'benefit' of orienting attention on valid cue trials, and the 'cost', on invalid trials, of having to disengage attention from the cue before reorienting to the target (Posner, 1980). If orienting to the cue is impaired, one would expect a smaller validity effect. This is the pattern found for vertical orienting in the PSP patients.

Inspection of figs 2 and 3 shows that, although the validity effect is smaller in the vertical plane at all cue-target intervals, this difference is greater for the early cue-target intervals. There is no evidence of orienting (i.e., no validity effect) until the 150 ms cue-target interval for arrow cues, and until the 350 ms cue-target interval for box cues. Thus not only is the validity effect smaller in the vertical plane in PSP patients, but it emerges with an increased latency. Although this interaction with interval was not statistically significant in the current experiment, it is consistent with the results of our earlier pilot study in 4 other PSP patients (Posner *et al.*, 1982). In that study no vertical validity effect was present until the 1000 ms cue-target interval. The failure to identify a significant interaction with interval in the current experiment may have been due to the failure to probe at longer cue-target intervals. Also, we do not know whether the smaller vertical validity effect is due to less efficient orienting on all trials, or the average of efficient orienting on some trials and no orienting on others. If the latter is the case, and if it is the percentage of trials with effective orienting which increases at longer cue-target intervals, than the large variability for valid vertical trials at short cue-target intervals might be too large to permit a statistically significant interaction with interval.

The current experiment was designed to test the hypothesis that midbrain pathways are involved specifically in orienting to exogenous signals. We speculated that endogenously-controlled orienting could be mediated by the cerebral cortex independent of the colliculi. However, the results from the arrow cue condition (fig. 3) clearly demonstrated that PSP patients are impaired in orienting attention endogenously in the vertical plane. This observation indicates that midbrain pathways are necessary for endogenous orienting of visual attention, and is consistent with the results of a similar experiment in split brain subjects. Holtzman *et al.* (1984) showed that, when commisurotomy patients were presented a spatial cue to one hemisphere, the opposite hemisphere was able to use the information to orient attention. The split brain result thus indicates that subcortical systems can be used to orient attention endogenously, while the PSP result indicates that midbrain function is necessary for this function. Nevertheless, comparison of figs 2 and 3 suggests that midbrain lesions may affect exogenous orienting more than endogenous orienting. The validity effect was smaller, relative to horizontal, and emerged after a longer latency in the exogenous (box) cuing than in the endogenous (arrow) cuing condition. We conclude that midbrain pathways are involved in both endogenous and endogenous orienting, but that exogenous orienting may be more vulnerable to midbrain lesions.

### *Comparison of orienting in PSP with parietal and thalamic lesions*

The results of the current experiment contrast with those reported previously in patients with parietal lesions (Posner *et al.*, 1984) and, together, they suggest that midbrain centres and cortical centres make independent and complementary contributions to the orienting of attention. Posner *et al.* (1984) have advanced a computational model for orienting of attention which specifies a division of labour between parietal and midbrain contributions. According to that model, there are three elementary operations involved in orienting visual attention: first attention must '*disengage*' from the current location, then '*move*' to a new location and then '*engage*' the new spatial position.

These elementary operations can be specified, operationally, using the kind of experiment employed in the current study (*see* fig. 1). While the subject is awaiting the presentation of the cue, the eyes are fixed in the centre but, since there is no stimulus there and no targets are expected there, attention is not engaged. When the cue is presented, the subject must move attention to the location indicated by the cue, and engage attention there in anticipation of the forthcoming target. The efficiency of moving attention can be inferred by facilitation of target detection, that is, the improvement in detection RTs on valid trials. Thus the relatively slower detection RTs in the vertical plane in PSP patients suggest that the peritectal lesions in this disease slow the moving of attention in the vertical plane.

On the other hand, if attention shifts to the cue, but the target then appears elsewhere (invalid cue condition), then attention must first disengage from the location of the cue before moving to the target. A deficiency of this disengage operation should then be reflected in a prolongation of detection RTs on invalid cue trials. PSP patients showed no difference between horizontal and vertical detection RTs on invalid trials; in fact RT for the vertical invalid condition tended to be quicker than those in the horizontal plane. These results do not, then, show evidence for any deficit in disengaging attention. On the other hand, since PSP patients did not orient efficiently to the vertical cues, we cannot conclude from these results that they can disengage normally.

Conversely, in patients with parietal lesions, cuing attention into the visual field contralateral to the lesion enabled them to detect targets there, on valid cue trials, almost as quickly as they detected targets with valid cues in the nonneglected visual field ipsilateral to the lesion. In striking contrast, their detection RTs on invalid trials were slowed dramatically in the visual field contralateral to the lesion (Posner *et al.*, 1984). Thus the pattern of results in parietal patients is the opposite of those reported here for midbrain dysfunction. In PSP patients the validity effect in the affected direction is smaller, whereas in parietal patients it is larger. The smaller validity effect in PSP patients is due to a slowing of RT for the valid cue condition, whereas the larger validity effect in parietal patients is due to a slowing of RT in the invalid cue condition. These results suggest that parietal lesions have little effect on the ability to *move* attention, but selectively affect the ability to *disengage* attention.

We have recently studied patients with thalamic haematomas in this experiment (Rafal and Posner, 1987). Thalamic patients have a pattern which is different from either PSP or parietal lesion. For the short cue-target intervals, the validity effect was larger in the contralesional visual field. In this regard thalamic lesions appear to affect the disengage operation in a way similar to parietal lesion; however, this disengage defect was much smaller and less persistent than with parietal lesions. The dominant abnormality in the thalamic lesion patients, which distinguished them from both PSP and parietal lesion subjects, was a large main effect of visual field; that is, RTs for contralesional targets were dramatically slowed for *both* valid and invalid cue conditions. This large main effect of visual field was present even though the patients had intact visual fields on perimetry testing, and none had severe clinical neglect. This result suggests that the thalamus may be necessary for the operation of *engaging* visual attention.

To summarize, we have been using this experimental paradigm to investigate cortical and subcortical structures which constitute a distributed network for the allocation of visual attention. This approach has confirmed that lesions of the midbrain, thalamus and parietal lobes all produce impairment in orienting covert visual attention. More importantly, however, this approach has revealed distinctly different patterns of defect from these three types of lesions, and permit us to speculate that each is coordinated with the other in mediating a specific elementary operation necessary to orient visual attention: the parietal lobe disengages attention; the midbrain mediates the move operation; and the thalamus is necessary to engage visual attention.

### *Midbrain integration of attention and eye movements*

In addition to their role in moving attention, midbrain pathways are also important in linking attention with eye movements, especially those activated by exogenous visual signals. When an exogenous signal triggers a saccade, attention is shifted to the target *before* the onset of the saccade (Posner, 1980). This movement of attention is time locked to the appearance of the target with a latency of 50–100 ms. The time course of these attention movements is similar to that reported for selective enhancement in monkey superior colliculus neurons in responding to an eccentric luminance change which served as the target for a saccade (Goldberg and Wurtz, 1972; Wurtz and Mohler, 1976).

An eccentric luminance change not only summons covert attention, but also primes the oculomotor system to prepare a saccade towards it. Posner and Cohen (1980) demonstrated that saccadic priming is activated through the retinotectal pathway in an experiment which took advantage of the different neuroanatomical connections of the subcortical retinotectal pathway, and of the cortical geniculostriate pathway. The geniculostriate system is binocular, and nasal and temporal hemiretinae are equally represented in the occipital cortex. In contrast, the extrageniculate system is dominantly monocular. The retinotectal pathway is crossed and each superior colliculus receives direct afferent input mainly from the contralateral eye. Moreover, in each superior colliculus the visual field of the contralateral eye is asymmetrically represented such that input from the temporal hemifield dominates, whereas little information from the nasal hemifield is mapped on the colliculus (Hendrickson *et al.*, 1970; Hubel *et al.*, 1975; Pollack and Hickey, 1979). In Posner and Cohen's experiment, normal subjects were presented simultaneous, bilateral peripheral targets, and instructed to move their eyes towards whichever felt 'natural and comfortable'. With binocular viewing, saccades occurred equally towards the two targets. Under monocular viewing, however, there was a strong bias (80%) to saccade towards the target in the temporal hemifield.

Thus exogenous visual signals both automatically summon attention and activate the retinotectal system to prepare a saccade. These effects of visual signals on attention and eye movements have also been shown to be biphasic. The initial facilitory effects of an exogenous signal on attention and eye movements are followed by a subsequent inhibition which slows detection at, and induces a bias against making a saccade towards the same location. Posner and Cohen (1984) demonstrated this 'inhibition of return' in an experiment in normal subjects. In that experiment a peripheral luminance change was followed by the brightening of a box in the middle of the screen summoning attention back to the centre. Then the target appeared either at the first cued peripheral location or, with equal probability, in the contralateral box. The results were *slower* detection RTs at the location of the first cue.

The inhibition of return also appears to be mediated by the retinotectal pathway. In normal human subjects tested under monocular conditions, the inhibition of return was larger in the temporal hemifield (Rafal and Inhoff, 1986). In a previous experiment in PSP patients, Posner *et al.* (1985) showed that the inhibition of return was present in the horizontal plane, but not in the vertical plane. The inhibition of return was present in both horizontal and vertical planes in parkinsonian controls; and there was no loss of inhibition of return contralateral to cortical lesions in frontal, parietal or temporal lobe lesion control subjects. Thus the inhibition of return appears to be an important midbrain mechanism for integrating attention and eye movements by biasing the oculomotor system to favour novelty.

The clinical observations on orienting in PSP (Rafal and Grimm, 1981) and the experimental observations reported here and by Posner *et al.* (1985) indicate that the phylogenetically older midbrain visual system continues to make an important contribution in regulating visually-guided behaviour in man. They converge with animal lesion studies demonstrating deficits in orienting behaviour after large peritectal lesions in cats (Sprague and Meikle, 1965) and monkeys (Denny-Brown and Fischer, 1976). Observations on 'blindsight' in individuals with hemianopia due to occipital lesions may also provide evidence for a retinotectal perceptual capacity in man. For example, such patients can learn to make saccades to targets that they cannot 'see' (Zihl, 1980). Since the geniculostriate pathway is not functioning in these patients, this orienting behaviour is assumed to be mediated by the retinotectal pathway.

We conclude that midbrain visual pathways are integrated with other cortical and subcortical centres in a distributed network for mediating visual attention. These centres contribute separate elementary operations for orienting attention, and the midbrain appears to be involved specifically in moving attention in the visual field. The midbrain system may play a special role in reflex orienting to exogenous signals, and for linking these covert attention movements to oculomotor systems for overt orienting.

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# SOME PROPRIOCEPTIVE INFLUENCES ON THE PERCEPTUAL REPRESENTATION OF BODY SHAPE AND ORIENTATION

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## SUMMARY

Perception of the surface contour of the body is generally thought to depend on topographically organized neural maps of somatosensation in the thalamus and cortex. Recent neurophysiological studies indicate that these maps are potentially modifiable through alterations in their sensory input. We present evidence that the apparent shape and orientation of the body can be changed within seconds by using muscle vibration to generate proprioceptive misinformation about limb position. Depending on the position of the hands or feet in relation to the rest of the body and to the test chamber, it is possible to generate systematic perceptual distortions of the body and changes in the apparent orientation of the body. Some implications of these observations for the maintenance of an accurate body schema, for spatial orientation, and for the encoding of ocular position are described.

## INTRODUCTION

The neural representations related to the conscious perception of the body surface are often thought to be expressed in the multiple topographic maps of somatosensation in the thalamus and cortex. Such maps have been identified in the course of stimulation studies in the alert human undergoing surgery for the treatment of intractable epilepsy (Penfield and Jasper, 1954; Penfield, 1958; Penfield and Roberts, 1959) and in systematic experimentation on animals (Woolsey, 1952, 1958). The perception of the parts of the body in relation to one another—position sense—has long been held to depend on the activity of joint receptors, the unmyelinated Ruffini-type endings in the synovium of the joints, and their central representations in neurons of the thalamus and the somatosensory cortex (for critical discussions of this view, *see* Mountcastle, 1957; Mountcastle and Powell, 1959; Mountcastle and Darian-Smith, 1968; Burgess *et al.*, 1982; Matthews, 1982).

Relatively recently, however, the perception of limb position was shown to also be influenced by muscle afferent signals. When the body or tendon of a muscle is

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mechanically vibrated, for example at 100 Hz, the muscle reflexly contracts; this contraction, known as a tonic vibration reflex (TVR), is dependent on the heightened muscle spindle activity elicited by the vibration (Hagbarth and Eklund, 1966). If the motion of a limb moving under the action of a TVR is resisted, illusory motion of the stationary limb is experienced (Goodwin *et al.*, 1972*b*, *c*). For example, if the biceps brachii muscle is vibrated, the forearm will reflexly move into flexion because of the TVR in the biceps; but if the forearm is physically restrained, the forearm will be experienced as moving in extension. In these circumstances, the aberrantly high level of spindle activity in the vibrated muscle in relation to the patterns of alpha and gamma motoneuron innervation of that muscle is interpreted as stretch and the 'stretch' is referred to the joint or joints about which the vibrated muscle acts (Goodwin *et al.*, 1972*a*, *b*; McCloskey, 1978; Matthews, 1982). This means that muscle afferent signals influence position sense. In fact, by vibrating the appropriate muscles, it is possible to elicit illusory motion of the entire body in virtually any desired direction (Lackner and Levine, 1979). Moreover, physically impossible limb positions and configurations can occasionally be perceived during muscle vibration; during biceps brachii vibration, for example, an individual may feel his forearm extend to as much as 270°, a physically impossible motion (Craske, 1977; Lackner and Taublieb, 1984).

As more information about the role of muscle spindle afferents in position sense has been obtained, it has become clear that skeletomuscular control is actively tuned to the 1G terrestrial force background of Earth and that muscle spindles are crucial to this adaptive tuning (Lackner and Graybiel, 1981, 1984; Lackner, 1985). As a consequence, if locomotor movements of the body are made in gravitoinertial force fields greater or lesser in magnitude than 1G, then aberrant motion of both the body and the surface of support will be experienced. These illusory motions result because the normal relationships among patterns of alpha and gamma motoneuron activity, muscle spindle discharge level, and the resulting movements of the body have been altered. For example, during exposure to a 2G acceleration level, if an individual lowers his body in a deep knee bend, he will feel both that he has moved downwards too quickly and that the support surface has physically moved upwards under his feet. In this situation, the body is lowered by controlled lengthening of antigravity muscles. Because the effective weight of the body has doubled, greater than normal activation of the antigravity muscles will be required during the course of the movement relative to producing the same body movement in the normal 1G force background of Earth. Consequently, the level of spindle activity in the antigravity muscles will be too high for the rate at which the body is being lowered. This abnormally high level of spindle activity is interpreted as the knee joints being in greater flexion than they actually are and this flexion is 'attributed' to the deck of the aircraft having risen up against the feet, thus stretching the antigravity muscles of the legs (Lackner and Graybiel, 1981, 1984; Lackner, 1985). By contrast, misperceptions of self-motion and of support surface stability are not evoked if the relationship among alpha and gamma motoneuronal activity, muscle spindle feedback, and body motion is artificially manipulated in a 1G environment by loading the body with a heavy object (Lackner and Graybiel, 1981, 1984). This means that the altered relationship is attributed to support and transport of the object rather than to a change in overall body weight; in fact, the weight of external objects may be determined in part by the increased force demands involved in holding them and simultaneously maintaining balance (*see* Lackner and Graybiel, 1984; Lackner, 1985). DiZio and Lackner (1982) have provided additional evidence for skeletomuscular tuning to terrestrial force levels: during voluntary body locomotion if the pattern of visual feedback received is inappropriate for the voluntary stepping movements being made, then the character of the stepping movements will be misperceived in terms of frequency, direction, or amplitude, and in some cases apparent leg length.

Such observations indicate that more complex sensory interactions are involved in the determination of position sense than can be accounted for solely by isolated static topographic mappings of somatosensation. This conclusion is further strengthened by the existence of the following interaction: if apparent motion of one arm is induced by muscle vibration and that arm is then grasped with the hand of the other arm, the apparent motion and displacement of the vibrated arm will be eliminated and the nonvibrated arm will be experienced as stationary. By contrast, if vibration is initiated after the arm to be vibrated has already been grasped, then both arms will be experienced as moving and changing position (Lackner and Taublieb, 1983). Thus information about the spatial configuration of the different parts of the body in relation to one another is taken into account when their position sense representations are assigned.

In this communication, our interest has been to explore the extent to which the apparent position or different parts of the body can influence the perception of body configuration and the position of the body in relation to its spatial surroundings. Our approach was to use muscle vibration as a way of distorting the apparent orientation of one or more limbs of the body while having the body positioned in different ways in relation to itself and to the test chamber. The test configurations were chosen so that changes in apparent limb position would in some cases be expected to influence body configuration and in others to affect the apparent orientation of the body within the test chamber. The findings demonstrate an extraordinary lability in the representation of orientation and in the representation of the dimensions and spatial contours of the body.

## METHODS

### *Subjects*

Ten men and 4 women between 18 and 30 years of age were paid for their voluntary participation, and informed consent was obtained from each volunteer. They were without sensory or motor abnormalities and had been screened to ensure that they had brisk TVRs in their biceps brachii, triceps brachii, triceps surae, and quadriceps femoris muscles.

### *Procedure*

Each subject participated in two experimental sessions, each lasting approximately 90 min During testing, a subject's eyes were blindfolded because sight of the body or of the test chamber attenuates or eliminates vibration-induced illusions of movement (Goodwin *et al*, 1972*a*, *b*; Lackner and Taublieb, 1983, 1984). In all the experimental situations, muscle vibration was achieved with hand-held electromagnetic physiotherapy vibrators, 120 pulses/s. Trial duration was 3 min and latency to onset of report of illusory motion or displacement was measured by a stopwatch. Each test configuration involved two trials: in one trial, a particular muscle or muscle pair, e.g., biceps brachii, was vibrated unilaterally or bilaterally; in the other trial, the antagonist muscle or muscle pair was vibrated. The orders of trials within a configuration (e.g., biceps brachii vs triceps brachii vibration) was vibrated unilaterally or bilaterally; in the other trial, the antagonist muscle or muscle pair was vibrated. The order of trials within a configuration (e.g , biceps brachii vs triceps brachii vibration) was balanced across subjects. Trials were separated by 5 min rest periods. During a trial and immediately afterwards, subjects were required to describe any changes in body orientation or illusions of arm movement (Lackner and Taublieb, 1983, 1984) and, thus, were experienced in making subjective reports; however, they were not aware of the rationale underlying the present study. Their responses were tape recorded for later analysis After each trial, the subjects also drew the patterns they had experienced.

## EXPERIMENTAL CONFIGURATIONS AND RESULTS

Ten experimental configurations were evaluated and the results are described in detail below for each configuration. Some general features or principles which unify the findings are best described first. In all of the test situations, the patterns reported by the subjects all represent meaningful interpretations or resolutions of the overall stimulation context present. Secondly, subjects commonly reported a dissociation between apparent movement and apparent displacement during vibration. The limb(s) or parts of the body that were undergoing motion seemed to displace spatially less than their apparent velocities would warrant. Moreover, peak apparent displacements were achieved while the involved body parts continued to be perceived as moving but no longer displacing further. Thirdly, given the patterns that were reported, it is clear that in situations involving contradictory information about limb position and about the surface contour of the body, the surface is perceptually distorted to become compatible with the representation of limb position. This means that physically impossible body configurations and dimensions can be represented perceptually. The bizarre sensations that can result, for example, stretching of the nose (fig. 1,1A) or shrinking of the waist (fig. 3,10B), have no discomfort associated with them. The subject does not feel that his nose is being painfully stretched by his hand or that his waist is being pinched in by his hands. Instead, there is a sense of wonder as the dimensions of the body are perceived to change; as one subject reported in test configuration 1A: 'Oh my gosh, my nose is a foot long! I feel like Pinocchio.'

The test configurations and results are described below and illustrated in figs 1–3, panels 1 to 10, which are keyed to the 10 test configurations. The average latencies to the onset of illusory motion for the test configurations are presented in the Table.

TABLE AVERAGE LATENCIES (IN s) FOR TEST CONFIGURATIONS 1–10

| *Trial* | *1* | *2* | *3* | *4* | *5* | *6* | *7* | *8* | *9* | *10* |
|---|---|---|---|---|---|---|---|---|---|---|
| A | 9.2 | 17.8 | 12.6 | 13.3 | 8.5 | 10.8 | 6.5 | 12.9 | 14.1 | 10.2 |
| B | 6.0 | 15.1 | 12.5 | 14.6 | 9.3 | 11.9 | 9.9 | 9.0 | 21.6 | 7.1 |

The average latencies to the onset of illusory motion of the body parts are presented for the 10 test configurations The A and B entries are for the different trials. for configurations 1,2,3,4,8,9 and 10, A = biceps brachii vibration, B = triceps vibration, for 5, A = trial 1, B = trial 2 of biceps brachii vibration; for 6, 7, A = achilles tendon vibration, B = rectus femoris vibration

### *1. Subject grasping his nose*

The subject was seated and grasping his nose with his right index finger and thumb; his right elbow was supported by an armrest. He was positioned such that if his forearm physically moved into extension, it would have pulled his nose away from his head, movement into flexion would have pushed his nose inward. The right biceps brachii was vibrated in test configuration A and the right triceps brachii in configuration B.

A. *Biceps brachii vibration* (fig. 1,1A). Of the 14 subjects, 10 experienced their arms moving into extension (average latency 9.2 s): 5 of these 10 experienced their noses as elongating, by as much as 30 cm, in keeping with the apparent motion of their hands; 3 experienced their fingers as elongating but not their noses, and 2

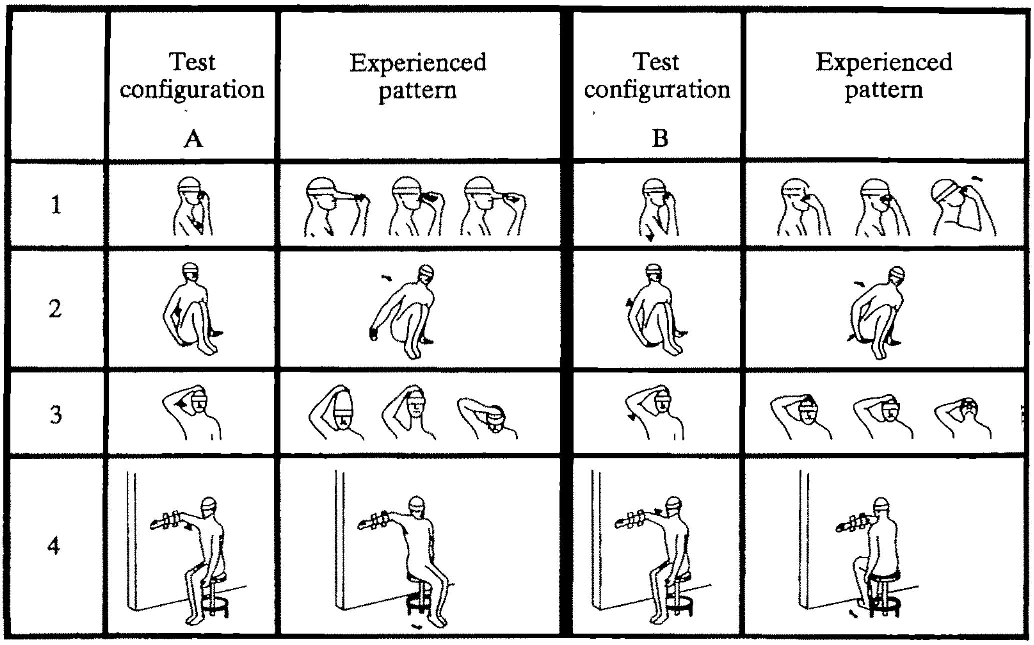

FIG 1. Each of the rows (1–4) represents a different experimental condition and the separate test configurations (A and B) for that condition (*see* text). The physical test situation is illustrated on the left for each configuration and then on the right the predominant patterns that were experienced during vibration Arrow head = placement of vibrator.

experienced their fingers and noses as elongating. The other 4 subjects each experienced a different pattern: tension on the arm and nose but no movement, apparent movement of the arm and nose without displacement, increased pressure of the fingers on the nose, and the final subject felt his arm tilt his head backwards.

B. *Triceps vibration* (fig. 1,1B). Thirteen of the subjects experienced their forearms as moving into flexion (average latency 6.0 s); 6 felt their noses had been pushed inside their heads; for 3, their fingers seemed to have passed through their noses and to be located inside their heads; 1 felt his fingers and nose 'melt' together; and 3 felt their heads had been tilted backwards by the pressure of their fingers on their noses. The remaining subject reported increased tension in his nose and fingers but no motion or displacement.

### 2. *Subject seated on floor with right hand under right buttock*

The subject was seated upright on the carpeted floor of the experimental room with his right hand, palm up, under his right buttock. The biceps and triceps brachii muscles of his right arm were vibrated separately, configuration 2A and 2B, respectively.

A. *Biceps brachii vibration* (fig. 1,2A). Twelve of the subjects experienced apparent extension of their forearms (average latency, 17.8 s): 9 experienced tilting of their heads and bodies away from their arms, by as much as 30°; 1 experienced his arm elongating; 2 experienced the floor as moving downward and their buttocks as elongating as their arms moved into extension. The other 2 subjects did not experience apparent motion of either arms or body.

B. *Triceps vibration* (fig. 1,2B). Twelve reported apparent forearm flexion (average latency 15.1 s); 10 felt their bodies tilting as much as 30° to the opposite side and being lifted by the apparent motion of their right forearms and hands; 1 experienced a lifting of his right buttock and leg of 15 to 20 cm without displacement of the rest of his body; and 1 reported arm flexion without apparent motion of the rest of his body. The remaining 2 subjects experienced neither arm nor body movement.

### 3. *Palm of right hand on the head*

The subject was seated with his right hand resting on and holding the top of his head. The biceps and triceps brachii of his right arm were vibrated in separate trials.

A. *Biceps brachii vibration* (fig. 1,3A). Of the 14 subjects, 13 experienced apparent movement of their forearms into extension (average latency, 12.6 s); 8 felt the tops of their heads had elongated, up to as much as 30 cm; 2 felt their heads rise because their necks seemed to have elongated; 2 reported forward tilt of their heads and lengthening of their forearms; and 1 reported movement of his forearm without change in apparent position.

B. *Triceps vibration* (fig. 1,3B). Thirteen subjects reported apparent flexion of their forearms (average latency, 12.5 s): 4 of them felt their fingers had moved down inside their heads; 5 felt the tops of their heads had been pushed down inside their heads by the motion of their hands; 3 felt their heads had been tilted 20° to 30° backwards by their hands, and 1 reported increased pressure on his head as his hand seemed to move downward without displacing. The remaining subject did not experience any changes.

### *4. Subject seated on rotatable stool, right arm strapped into holder on the wall*

The subject was seated on a rotatable stool that was locked in position (although he was unaware that it was locked); his right arm was strapped into an arm holder mounted on the wall of the experimental chamber. Physical flexion of his forearm would have resulted in a clockwise rotation of the subject on the stool, extension would have rotated him counterclockwise. The biceps and triceps brachii in his right arm were vibrated in different trials.

A. *Biceps brachii vibration* (fig. 1,4A). Thirteen subjects felt their arms move into extension (average latency, 13.3 s): 11 of them felt their forearms were stationary and their bodies had rotated away from their forearms as much as 90°; 1 felt no body movement, only arm motion; 1 felt his forearm and the wall to have moved away from his body. The final subject experienced no illusion.

B. *Triceps vibration* (fig. 1,4B). The same patterns that occurred with biceps brachii vibration were reported by the same subjects, but with reversed sign (average latency, 14.6 s).

### *5. Subject supine, forearms vertical*

The subject was lying on his back on the floor with his upper arms horizontal and his forearms orientated vertically and restrained in position. The biceps brachii muscles were vibrated bilaterally in both trials.

A, B. *Biceps brachii vibration* (fig. 2,5A). Thirteen subjects reported that their forearms moved downwards into extension (average latency, 8.5 s first trial, 9.3 s second trial): 9 reported that as their forearms 'moved' into extension their torsos seemed to move backwards and downwards up to 45°; 4 felt their torsos had risen as much as 25° during vibration, thereby decreasing the degree of apparent forearm extension while also moving the forearms towards the floor. The remaining subject experienced no changes in orientation.

### *6. Subject lying on his back, thighs vertical, lower legs horizontal, feet against the wall*

The subject was lying on his back with his thighs vertical and his lower legs horizontal; his feet were flat against a wall of the experimental chamber. The achilles tendons and the rectus femoris of the quadriceps femoris muscles were vibrated bilaterally in separate experimental trials.

A. *Achilles tendons vibration* (fig. 2,6A). Twelve of the subjects experienced apparent motion of their legs and feet (average latency, 10.8 s): 8 of them felt their legs go into full extension at the knees with their lower legs tilting the wall up and toward them; 6 of these 8 also felt an approximately 20° backward body rotation

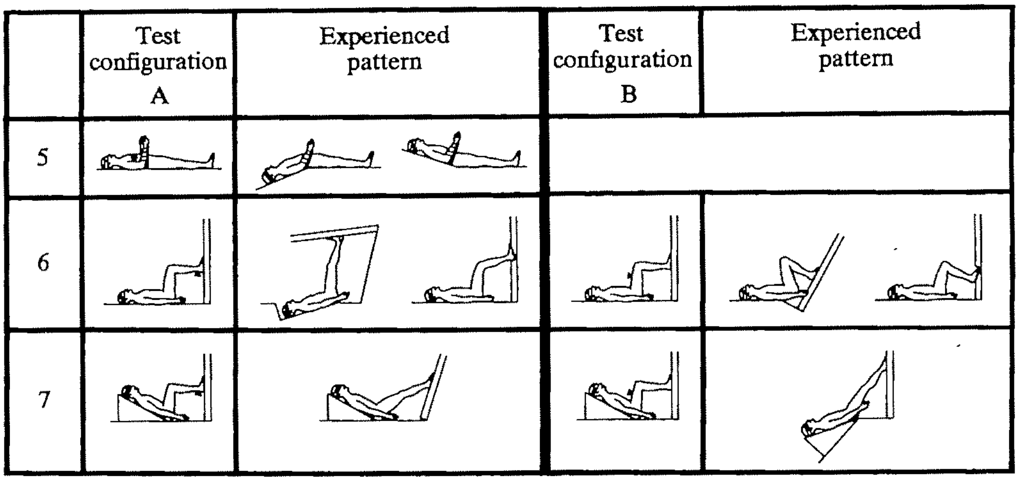

FIG. 2 Each row (5–7) represents a different experimental condition and the test configurations used (*see* text). The predominant patterns experienced during vibration are presented to the right of the illustrations of the test configurations. Condition 5 involved bilateral vibration of the biceps brachii muscles twice for each subject. Arrow head = placement of vibrator.

with the pivot point at the hips; the other 4 subjects experienced their heels as having pushed several centimetres into the wall as their legs 'extended' at the knees. The remaining 2 subjects reported neither illusory motion nor displacement.

B. *Rectus femoris vibration* (fig. 2,6B). Thirteen of the subjects reported motion of their feet and legs (average latency, 11.9 s): 9 felt their legs flex up to 45° at the knees so that their lower legs seemed to move downwards and tilt the wall away from them; 7 of the 9 also felt upwards body rotation of approximately 20° with pivoting at the hips; the other 4 felt their toes had moved into the wall as their lower legs seemed to flex. The remaining subject experienced no changes during vibration.

*7. Subject with head and back at 30° angle to floor, feet on wall*

The subject was lying supine with his head and back supported at a 30° angle with the floor; his thighs were vertical and his lower legs horizontal with the feet flat against a wall of the experimental chamber. The achilles tendons were bilaterally vibrated in one trial and the rectus femoris of the quadriceps muscles in the other.

A. *Achilles tendon vibration* (fig. 2,7A). All 14 subjects reported apparent motion of their legs or feet into extension (average latency, 6.5 s): 5 of them felt as if their lower legs straightened and their feet moved through the wall; the remaining 9 subjects felt the wall had been tilted or displaced away by the action of their feet; 2 of these subjects had felt a backward body rotation of approximately 30° with pivoting from the hips, as well.

B. *Rectus femoris vibration* (fig. 2,7B). Thirteen subjects experienced apparent motion of their legs and feet (average latency, 9.9 s): 9 of these felt as if their bodies

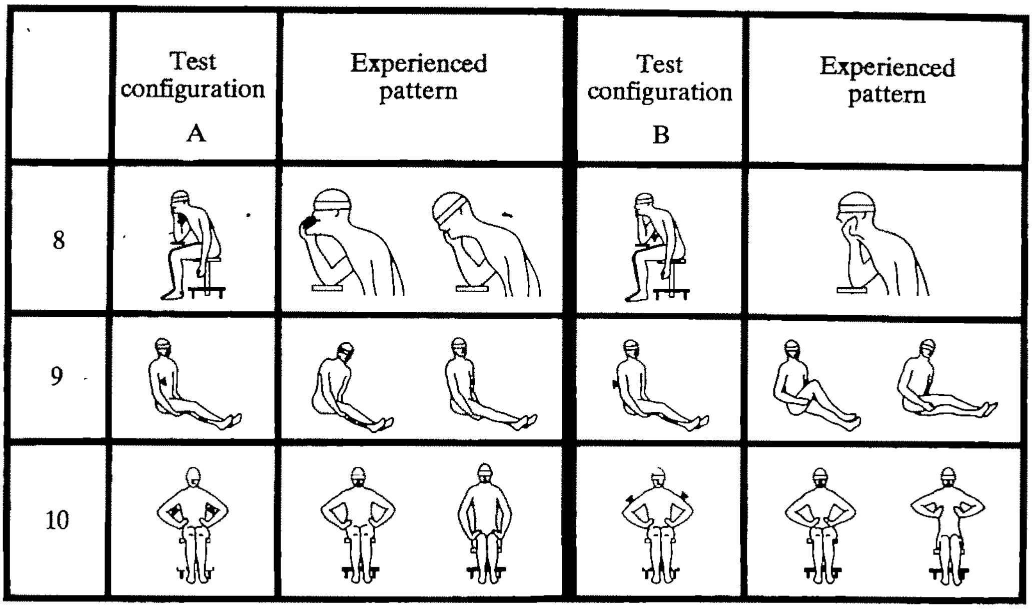

FIG. 3. The rows (8–10) illustrate the different test conditions and the test configurations within each condition (*see* text). The predominant patterns experienced during vibration are presented to the right of the figures depicting the physical configuration of the body and the position of the vibrator(s). Arrow head = placement of vibrator.

rotated backwards from the hips up to 40°; 1 of the 9 felt he had done a complete somersault backwards while the walls seemed to have remained stationary; 4 experienced either their knees as having straightened out and their feet as having gone through the wall (1), pushing and tilting of the wall (2), or a lost awareness of the spatial position of the feet (1). The remaining subject did not experience apparent motion.

### 8. *Subject seated, chin in right hand*

The subject was seated with his right elbow resting on an arm support and leaning so that his chin and head were supported by the palm of his right hand. The right biceps and the right triceps brachii muscles were separately vibrated.

A. *Biceps brachii vibration* (fig. 3,8A). Ten subjects experienced their hands and forearms moving into extension (average latency, 12.3 s): for 6 of these, their chins seemed to have stretched or elongated many centimetres so as to maintain contact with their hands; 4 experienced their heads or heads and torsos as having tilted forward slightly, 5 to 10°, so as to maintain hand contact. Of the remaining 4 subjects, 2 experienced a decrease in apparent pressure on the chin, 1 felt his chin had disappeared, and the final subject reported no changes during vibration.

B. *Triceps vibration* (fig. 3,8B). Eleven subjects felt their forearms move into flexion (average latency, 9.0 s): 9 of them experienced their hands as having pushed their chins into their heads so that their chins felt near the centre of their heads; 1

experienced his forearm to be shrinking as it 'moved' into flexion thereby allowing the apparent position of his chin to have remained unchanged; 1 felt that his fingers had moved through his chin into his head. Two subjects reported their elbows had twisted clockwise 90° as a result of the 'flexion' of the forearm and the pressure of the chin on the hand. One subject reported no changes.

### *9. Subject seated on floor, right hand under right thigh*

The subject was seated on the floor with his legs outstretched and crossed, right over left; his right hand was under his right lower thigh, palm up. In one trial, the triceps brachii muscle of the right arm was vibrated; in the other, the biceps brachii.

A. *Biceps brachii vibration* (fig. 3,9A). Eleven subjects reported extension of their forearms (average latency, 14.1 s): 7 felt the 'extension' of their arms had tilted their bodies as much as 45° to the opposite side; 3 felt their knees had moved down with their hands; 1 felt his knee had pushed his hand down. The remaining 3 subjects either experienced no illusions (2) or motion of the arm with the leg remaining stationary.

B. *Triceps vibration* (fig. 3,9B). Ten subjects reported arm flexion (average latency, 21.6 s): 5 felt their forearms pull their upper legs and knees towards their chests; 4 felt their arms had lifted the same sides of their bodies up many centimetres from the floor; 1 felt his forearm and elbow had stretched to 'allow' his thigh position to remain unchanged. The remaining 4 failed to experience illusions.

### *10. Subject seated arms akimbo*

The subject was seated on a stool with his hands on his waist, arms akimbo. The biceps and the triceps brachii muscles were vibrated bilaterally in separate trials.

A. *Biceps brachii vibration* (fig. 3,10A). Of the 14 subjects, 12 experienced apparent extension of both their arms (average latency, 10.2 s): for 5 it seemed as if their waists had expanded 15 to 30 cm in diameter to keep pace with the apparent displacements of their hands; 5 felt that their torsos had become elongated 25 to 30 cm because their hips had displaced downwards and their torsos upwards owing to the motion of their hands; 2 felt their arms had elongated at the shoulders without any hip or waist changes; 1 felt that his arms had pivoted forwards as they extended and that there was less pressure on his waist. One subject did not experience illusions.

B. *Triceps vibration* (fig. 3,10B). Eleven subjects reported apparent flexion of their arms (average latency, 7.1 s): 5 of them felt their forearms and hands had moved inwards, compressing their waists by as much as 25 cm until they had wasp-like waist lines; 6 felt their forearms and hands had moved upwards, pushing their torsos up while their hips and legs stretched downwards until their bodies were elongated by 20 to 30 cm in the midriff region. Three subjects did not experience illusory displacements of their arms but reported an increase in pressure on their waists without any changes in body configuration.

In each of the test configurations, 1 subject tended not to experience illusory motion or displacement of his arms or of parts of his body. This was always the same individual.

## DISCUSSION

Our observations demonstrate that vibration-induced illusions of limb motion can affect the somatosensory representation of the body and the apparent position and configuration of the body in relation to its surroundings. Virtually all the patterns reported represented synergistic interpretations of the patterns of stimulation present. Although some of the effects experienced represent physically impossible situations, such as lengthening of the nose to 30 cm, they nevertheless are 'good solutions' in that they are a direct and meaningful response to the prevailing patterns of stimulation. For example, regardless of test configuration, vibration of the biceps brachii was associated with illusory extension of the forearm and the experienced configuration of the rest of the body was always one understandable in terms of the perceived forearm extension being interpreted as actual extension of the arm. This principle was apparent in each test situation: vibration-induced illusory motion and displacement of body appendages was treated as true motion and so interpreted in relation to the rest of the body.

An important aspect of our findings is the demonstration that the perceptual representation of the shape of the body is highly labile. Earlier work had shown that apparent limb position could be readily distorted by providing abnormal patterns of muscle spindle activity (Goodwin *et al.*, 1972*a*, *b*; McCloskey, 1978; Matthews, 1982). The findings presented here show that the length of different parts of the body, such as the nose, can be affected by the apparent position of other body parts. In the situations in which the nose was being held and the biceps or triceps brachii muscle was vibrated, the following 'computations' must have taken place: (1) the abnormally high level of spindle activity was attributed to stretch of the vibrated muscle and interpreted as movement of the forearm into extension or flexion; (2) the patterns of somatosensory stimulation present indicated that the fingers of the hand and the nose were in contact; (3) the forearm can move with the hand maintaining contact with the nose only if the nose is also moving; (4) sensory and motor information about head position indicated that the head was stationary; (5) consequently, the nose had to be 'represented' as changing length or position, or the hand and fingers as elongating, because these are the only interpretations consistent with the hand and nose maintaining physical contact while the hand is moving and the head stationary.

Similar abstract computations must be related to the perceived shrinking and expansion of the waist during triceps or biceps brachii vibration in the arms akimbo position of configuration 10; however, in this and our other test situations additional interpretations could have been equally meaningful. For example, the forearms could have been perceived as moving but not displacing with the hands maintaining contact with the waist; tactile stimulation of the surfaces of the hands and of the waist could have been experienced with the hands and the waist being perceived in different spatial positions; or the hands and waist could have been perceived as stationary and in contact. In this last alternative, somatosensory spatial information about the part of the body touched by the hands would have 'overridden' the aberrant representations of limb positions.

In the present study, the latencies to the onset of illusory motion were usually much higher than those observed in our earlier studies in which the onset of illusory motion of the arm was measured for biceps and triceps brachii stimulation under conditions in which the hand was not in contact with any other part of the body (Lackner and Taublieb, 1983, 1984). These longer latencies probably mean that the sensory interactions created in the different test situations of the present study require time for their resolution. Until this resolution begins, changes in apparent orientations are not experienced. For example, Goodwin *et al.* (1972*c*) found latencies on the order of 1 s for vibration-induced illusions of limb movement alone. The present situation involving more complex interactions accordingly involve much longer latencies.

The position and configuration of the body in relation to the test chamber also clearly affected the patterns of illusory motion experienced. For example, in test configurations 5, 6 and 7, in which the subject's head and torso were horizontal or 30° from the horizontal, considerable upward or backward displacement of the head and torso was often reported. Such changes in perceived head position can be accounted for by considering the minimized contribution of the linear acceleration-sensitive receptors of the inner ear, the otolith organs, in affecting the registration of head position in these test situations. When the head is close to the horizontal rather than the gravitational vertical, the otolith organs are less effective in indicating head position in relation to the direction of gravity (*see* Graybiel and Patterson, 1955; DiZio and Lackner, 1986). This should render apparent head position more susceptible to reinterpretation than when the head is physically vertical (Lackner and Levine, 1979). In configuration 4, the subject was seated on a rotatable stool and when the biceps or triceps brachii muscle was vibrated, the resulting illusory motion at the elbow joint tended to be perceived as rotation of the subject's body on the stool rather than as movement of the wall to which the subject's forearm was strapped. In this situation, the unchanging input from the semicircular canals would be consistent with constant velocity rotation about the elbow joint (*see* Lackner and Levine, 1979; Lackner, 1981, 1985). Accordingly, perceived constant velocity motion of the body and upper arm in relation to a stationary forearm was a meaningful interpretation of the actual patterns of stimulation.

Throughout the experimental findings, the occurrence of 'good solutions' to the prevailing patterns of stimulation and to the configurations of the body in relation to the experimental chamber is apparent. These solutions, although often involving impossible physical configurations of the body, such as the nose stretching or the head telescoping into the torso, nevertheless are meaningful in terms of the ongoing patterns of stimulations. Their nature helps us to understand better the ways in which the representation of the position sense of the body is organized. The representation of limb position clearly can affect the apparent length and size of the parts of the body and it simply does not seem to matter if physically impossible configurations are perceptually specified. Rather, in the perceptual representation of the body surface and configuration, the mobile parts of the body, especially the limbs, seem to have representational priority. Physical coincidence of body surfaces indicated by somatosensory information is important while physical continuity itself is not. For example, with the hand positioned on top of the head and triceps brachii vibration, the hand was perceived as displacing and physically pushing the head into the trunk, despite the head being in physical continuity with the trunk through the neck.

The dimensions and shape of the body have long been thought to be coded in the activity patterns of topographic somatosensory maps in the thalamus and cortex. Within this neural framework, limb length and trunk contours are represented by the discharge patterns of neurons in particular areas of the neural maps. The ability to cause changes in perceived length of a body part by creating illusory motion of another body part in physical juxtaposition indicates that more than the activity of somatotopic neural maps alone is involved in the perceptual specification of body configuration. Indeed, it is apparent that spatial information about other parts of the body is also implicated, and that position sense and the body schema represent a collaborative interaction of multiple afferent and efferent domains which can result in a multitude of apparent positions and orientations, real or illusory, being generated.

In this context, it is notable that Kaas and his colleagues (Kaas, 1977, 1983; Merzenich *et al.*, 1978; Kaas *et al.*, 1979, 1981) and other investigators (Kalaska and Pomeranz, 1979) have shown that there is considerable plasticity in the neuronal representation of the body surface in somatosensory cortex; in fact, the cortical maps of somatosensation are modifiable. For example, Kaas *et al.* (1981) reported that although during the course of a recording session the receptive fields of particular neurons may remain fixed, '... it also appears that this stable organization is a result of balancing dynamic influences. When this balance is disrupted by inactivating part of the peripheral sensory input, the organizations of the cortical maps are immediately altered and continue to change over time' (p. 256). Thus, as they point out, even in the adult the maps of somatosensation are dynamically organized and potentially modifiable.

It is tempting to speculate that in our experiments we have developed a way of reversibly modifying cortical maps of somatosensation through systematic distortion of the sensory input. Regardless of the value of this speculation, which can be evaluated in animal preparations, our results point to the great modifiability of the perceptual representations of the body surface in the adult human; perceptual remappings can be generated within seconds. The fact that the mobile parts of the body seem to have representational priority in affecting the body schema may also have considerable functional significance. In the course of development, the dimensions of the body change greatly; these changes continue to a lesser extent in adulthood with variations in body mass being a relatively common occurrence and other changes, such as a gradual diminution in height, being less frequent. The question arises as to how the position sense of the body and the body schema is kept accurately calibrated over time. That is, how are the 'maps' underlying position sense and somatosensation recalibrated to take into account changes in body dimensions?

One can envisage position sense being updated on the basis of sensory-motor transactions. For example, if an object is seen in a particular position and a reaching movement is made, the success of the reach depends on the arm being configured in such a way as to bring it into appropriate contact with the object. In this situation, there is a dynamic interplay of motor innervation and sensory feedback that provides for the updating of control variables that must include such factors as the current dimensions and masses of the various parts of the limb and the body and the efficiency of the arm muscles and support musculature. Accordingly, in principle, position sense of the independently mobile parts of the body can be maintained through transactions with the environment. The rest of the body is not subject to the same degree of interaction with the external environment and it may be that its somatosensory representation is updated by contact with the motile appendages of the body, as suggested by the present evidence.

These reformulated notions of position sense can be applied in another domain, oculomotor control. It is known that the apparent position of the eyes can be influenced by information about limb position (Lackner, 1981, 1985; Lackner and Levine, 1978, 1979, 1981; Levine and Lackner, 1979) and furthermore that such brachial proprioceptive information can be used to enhance fixation stability (Lackner and Zabkar, 1977; J. Evanoff and J. R. Lackner, unpublished observations). These observations are of interest because they suggest that limb-position information could be used in calibrating the direction of gaze of the eyes.

Of the motile parts of the body, the eyes alone do not seem to have effective afferent specification of position; instead, precise knowledge of moment to moment eye position appears to depend on monitoring efferent command signals to move the eyes (*see* Carpenter, 1977; Steinbach and Smith, 1981). However, it is necessary to adjust these command signals over time to take into account variations in metabolic activity of the extraocular muscles, changes in muscle efficiency, and so on (Ludvigh, 1952*a*, *b*). Sight of the hand would allow eye position control to be updated as necessary because the position of the hand and other parts of the body can be accurately determined in relation to the head, whereas the directions of external visual objects not in contact with the body cannot be independently specified.

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# ‘FRONTAL’ COGNITIVE FUNCTION IN PATIENTS WITH PARKINSON’S DISEASE ‘ON’ AND ‘OFF’ LEVODOPA

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## SUMMARY

A wide range of cognitive impairments can be observed in patients with Parkinson’s disease. A close parallel exists between these deficits and those found following damage to prefrontal cortex. Anatomical evidence is reviewed which reveals a complex pattern of neuronal circuits connecting the frontal cortex and basal ganglia. All these circuits are in some way dependent upon dopamine, suggesting that changes in the levels of dopamine stimulation may alter performance on ‘frontal’ tests. To test this hypothesis, a group of patients with Parkinson’s disease were assessed both on and off levodopa treatment, on a range of tests selected from the human and animal experimental literature as being sensitive to disruption of prefrontal cortex. A variable pattern of results was obtained. On one test, a measure of verbal fluency, patients were impaired, compared with normal controls, only when off levodopa. On two measures, associative conditional learning and subject-ordered pointing, patients were impaired only when on levodopa, while on the final measures, the Wisconsin Card Sorting Test, patients were impaired both on and off levodopa. Two mechanisms are discussed to explain these results, one based on the effects of dopamine depletion, and the other based on the adverse effects of dopamine overstimulation. The results suggest that different areas of prefrontal cortex are involved in the tasks employed, and that functional levels of dopamine in separate areas of cortex and caudate may differ crucially in Parkinson’s disease.

## INTRODUCTION

Research over the past two decades has produced an extensive body of evidence on cognitive function in Parkinson’s disease. The studies fall into two main categories. First there are those which reported a generalized intellectual deterioration (Reitan and Boll, 1971; Portin and Rinne, 1980; Pirozzolo *et al.*, 1982). While these group studies found the mean performances in Parkinson’s disease to be below the mean level of normal controls on a wide variety of tests, they placed no figure on the proportion of patients who might be considered to have a clinically significant dementia. The exact proportion is not clear, but a figure in the region of 10 to 15% may be a reasonable estimate (Brown and Marsden, 1984). The nature of the

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cognitive changes in the dementia of Parkinson's disease has yet to be clearly described. It is uncertain whether the dementia in Parkinson's disease forms one extreme of a continuous distribution of cognitive impairment, or represents a distinct subgroup. Until this issue is clarified, it is important to exclude any patient with dementia from studies of cognitive function in Parkinson's disease. The second class of studies are those which have found more subtle and specific deficits, mainly in nondemented patients (*see* Brown and Marsden 1987, for a review). Deficits have been reported in the areas of language (Matison *et al.*, 1982), memory (Warburton, 1967; Wilson *et al.*, 1980; Tweedy *et al.*, 1982; Flowers *et al.*, 1984), visuospatial function (Bowen *et al.*, 1972, 1976; Boller *et al.*, 1984), and concept formation and behavioural regulation (Bowen *et al.*, 1975; Flowers, 1982; Lees and Smith, 1983; Cools *et al.*, 1984; Flowers and Robertson, 1985).

Caution is necessary in inferring a true cognitive impairment from poor performance on neuropsychological tests. In Parkinson's disease, factors such as nonspecific age-related decline, impaired motor speed and manual dexterity, mental and physical fatiguability, depressed mood and drug-related confusional states, are all potential causes of poor performance. Careful assessment of such factors and the use of appropriate control groups are necessary before firm conclusions can be drawn. While many of the above studies did not control for all such factors, it seems that relatively subtle cognitive impairment is found in a proportion of even nondemented patients with Parkinson's disease. One area which has been receiving increasing attention is the parallel between the cognitive deficits shown by patients with Parkinson's disease, and those found following lesions to prefrontal cortex. 'Frontal' deficits shown by patients with Parkinson's disease include impaired delayed matching to sample (Horne, 1971), increased sensitivity to proactive interference (Tweedy *et al.*, 1982), increased spontaneous Necker Cube alternations and decreased ability to 'freeze' the cube (Talland, 1962), impaired performance in carrying out simultaneous motor tasks (Talland and Schwab, 1964; Horne, 1973), impaired prism adaptation (Canavan and Passingham, 1985; Stern *et al.*, 1986), impaired ability to reproduce a sequence of gestures (Morel-Maroger, 1977), impaired performance on conditional associative learning tasks (Canavan and Passingham, 1985), and impaired performance on the Wisconsin Card Sorting Test (Bowen *et al.*, 1975; Lees and Smith, 1983; Taylor *et al.*, 1986).

An explanation for this pattern of impairment has been sought in the close anatomical associations between the striatum and the frontal cortex. Evidence suggests that regions of the striatum are linked in neuronal 'loops' via thalamus to discrete regions of frontal cortex. DeLong *et al.* (1984) described two such loops, the first, the 'motor loop' linking the putamen with the supplementary motor cortex, and the second, a 'complex loop' linking the caudate with prefrontal cortex. The behavioural effects of selective lesions in animals suggests that the complex loop plays an important role in cognitive function. As early as 1956, Rosvold and Delgado showed, in monkeys, that performance on delayed alternation tasks, which are sensitive to damage to the prefrontal cortex, is impaired also by stimulation or coagulation of the head of the caudate. The intimate functional as well as anatomical association between prefrontal cortex and the head of the caudate has been shown in studies which found equivalent impairments following lesions to either region (Rosvold and Szwarcbart, 1964; Bossom, 1965; Divac, 1971). In a recent study by A. G. M. Canavan and others (personal communication), lesions were placed in various thalamic nuclei in monkeys. Lesions to nuclei involved in the caudatoprefrontal loop had a significant effect on cognitive function, unlike lesions placed in the thalamic nuclei involved in the motor loop. Together, this evidence suggests the hypothesis that the apparent 'frontal' picture found in Parkinson's disease may be attributed to disruption within the 'complex loop' (Taylor *et al.*, 1986; Brown and Marsden, 1987). This simple model, however, has been complicated by recent evidence which suggests that the striatum and frontal cortex are linked in not two but five or possibly more parallel but independent circuits (Alexander *et al.*, 1986). In addition to the previously described 'motor' loop, a second motor circuit responsible for the control of eye movement has been described. The remaining three circuits are defined purely anatomically as their functional significance has yet to be determined with certainty. The first is the 'dorsolateral prefrontal' circuit. The dorsolateral portion of the head of the caudate, and a rostrocaudal section extending to the tail, receives input from the dorsolateral prefrontal cortex, posterior parietal cortex and arcuate premotor area. Output from the caudate back to prefrontal cortex is via two routes. The first is via the globus pallidus and discrete thalamic nuclei to the caudal prefrontal region, the second via the substantia nigra and thalamus to the dorsolateral prefrontal cortex. The second prefrontal loop is the 'lateral orbitofrontal' circuit. This area of prefrontal cortex projects to the ventromedial sector of the caudate extending from the head to the tail. Output is again via two routes involving both globus pallidus and substantia nigra, which finally converge on lateral orbitofrontal cortex. The final circuit defined to date is the 'anterior cingulate' circuit. The ventral striatum (nucleus accumbens and olfactory tubercle) receives extensive projections from hippocampus and amygdala, as well as various areas of limbic cortex and neocortex (entorhinal, perirhinal, anterior cingulate and temporal cortex). Output from the ventral striatum is via the globus pallidus and substantia nigra to various regions including the anterior cingulate area, thus closing the loop.

Postmortem studies have revealed that the major structural damage found in Parkinson's disease is in the dopamine-producing cells of the substantia nigra, pars compacta. The impact of this cell loss is a widespread loss of dopamine in the striatum. In addition to the nigrostriatal system, the mesocorticolimbic dopamine system is also affected in Parkinson's disease. Cell loss in the ventral tegmental area leads to dopamine loss in limbic areas (nucleus accumbens, parolfactory gyrus, cingulate and entorhinal cortex, hippocampus and the olfactory tubercles), and neocortical areas (frontal, temporal and occipital cortex). The postmortem studies give some idea of the extent of the dopamine depletion in the different projection areas. Agid *et al.* (1987) have reviewed the available evidence. Dopamine depletion is greatest in the stratium with levels in the putamen being most markedly reduced to only 5% or less of normal values. The depletion in the caudate, while still marked, seems to be less extreme at 15 to 20% of normal levels. Nothing is known, however, of the relative levels of dopamine depletion in the separate areas of caudate involved in the different caudatocortical loops. It is possible that within individual patients, the regions of caudate involved in the lateral orbitofrontal and dorsolateral prefrontal circuits may be differentially depleted of dopamine. More detailed postmortem investigation is necessary to determine this point. Finally, dopamine levels in the projection areas of the ventral tegmental areas are least severely affected. Levels in the nucleus accumbens, hippocampus and frontal cortex are approximately 40% of normal, while levels in cingulate cortex, amygdala and hypothalamus are nearer 50% of normal.

That dopamine levels are depleted in both the nigrostriatal and the mesocorticolimbic systems, albeit to different degrees, suggests two possible mechanisms whereby dopamine depletion might interfere with cognitive function in Parkinson's disease. The first is via one or both of the lateral orbitofrontal and dorsolateral prefrontal circuits. Dopamine depletion would disrupt caudate function to impair basal ganglia input to prefrontal cortex. The second mechanism is a direct depletion of dopamine in areas of frontal cortex innervated by the ventral tegmental area. The functional significance of frontal dopamine depletion was shown by Brozoski *et al.* (1979). They injected 6-hydroxydopamine into the prefrontal cortex of monkeys and found impaired performance on a delayed alternation task.

Caution is necessary, however, in building models solely on the result of postmortem evidence. Because the average age of patients at death is generally much higher than that of subjects who take part in neuropsychological investigation, it can provide only a 'worst case' estimate of dopamine levels in life. Furthermore, absolute levels of dopamine do not necessarily indicate functional significance. Mechanisms such as increased dopamine turnover and receptor supersensitivity may allow moderately depleted dopamine levels to produce relatively normal neuronal and synaptic functional activity. The degree of compensation seems to be greatest in the striatum with increases in turnover of almost 700% in the putamen, and 300% in the caudate, compared with only 150% in frontal cortex (Scatton *et al.*, 1984). Recent evidence from PET scanning during life using 6-fluoro-levodopa, however, has confirmed the differential involvement of dopamine systems in the putamen and caudate in Parkinson's disease. Nahmias *et al.* (1985) assessed 11 patients, most having unilateral symptoms. None was on dopaminergic medication, and all were normal on a detailed neuropsychological assessment. Results revealed that while dopamine levels in the putamen contralateral to the affected side were reduced, levels in the head of the caudate were normal. In a study by Martin *et al.* (1986), dopamine levels in putamen were also severely decreased, with the decrease being greatest in the putamen contralateral to the side of maximum parkinsonian motor symptoms. Caudate dopamine levels were reduced, but to a far lesser extent than the putamen, with approximately half of the sample having levels within the normal range. Furthermore, caudate depletion was the same in both ipsilateral and contralateral caudates. No published study has yet assessed dopamine levels in frontal cortex, or looked at the neuropsychological correlates of dopamine levels as revealed by PET scanning. In general these data support the findings of maximal impairment in the putamen and related 'motor' structures, the caudate being less or more variably involved, with a large proportion of patients having normal levels. As with the postmortem data, however, evidence from PET scanning has provided no information on relative levels of dopamine in different regions of the caudate.

The significance of brain dopamine on cognitive function in man has been studied most frequently by assessing the effects of levodopa on cognitive function in patients with Parkinson's disease. A number of studies have assessed patients before levodopa treatment and at various stages thereafter (Riklan *et al.*, 1976; Portin *et al.*, 1984). Results show, on average, an initial improvement in cognitive function, followed eventually by a gradual decline. An alternative approach is to assess patients both on and off their normal medication. This permits greater experimental control over factors such as order of testing, and avoids confounding the effects of treatment with progression of the disease. Four previous studies have assessed cognitive function under 'on' and 'off' conditions. Brown *et al.* (1984) assessed verbal, spatial and numerical ability. While patients showed a deterioration in performance when 'off' levodopa, the change was related more closely to the patients' levels of mood and alertness than to their motor status and were mild relative to the severe changes in motor ability. Rafal *et al.* (1984) used a reaction time paradigm with cognitive tasks of increasing complexity. While patients were slower 'off' than 'on', there was no disproportionate slowing during the more complex tasks when 'off'. Girotti *et al.* (1986) employed a range of neuropsychological tests, assessing visual memory, verbal fluency, visuospatial function and attention. No significant difference was found between the 'on' and 'off' states. With the exception of verbal fluency in the latter study, 'frontal' function has received little attention in these 'on–off' studies. Delis *et al.* (1982), however, described a single case which offers some tentative support for the role of dopamine on 'frontal' function in Parkinson's disease, finding disinhibition in language and perseverative tendencies when off levodopa.

The present study aimed to assess the impact of fluctuations in brain dopamine levels on 'frontal' cognitive function in patients with Parkinson's disease, by testing them both 'on' and 'off' levodopa treatment. Because the frontal cortex does not have a homogeneous function, a range of tests were administered which previous human and animal research had indicated were sensitive to disruption of the frontal cortex.

## METHODS

### *Subjects*

Sixteen patients with a diagnosis of idiopathic Parkinson's disease were studied. All exhibited a typical akinetic-rigid syndrome, and 12 had classical rest tremor. All had shown a considerable response to levodopa treatment and continued to benefit. The subjects were regular outpatients at the Parkinson's disease clinic at King's College Hospital, and all were on optimum levodopa medication (mean daily dose of 1130 mg, range 500–3000 mg). All were aged less than 75 yrs and none had evidence of gross intellectual impairment. None of the subjects had undergone thalamotomy or had any history of stroke or brain injury. The sample comprised 12 males and 4 females, with a mean age of 64.4 yrs (SD 5.9) and mean duration of illness of 9.9 yrs (range 2–28 yrs).

The 16 control subjects were either spouses of the patients or were members of a subject panel. Seven males and 9 females took part, with a mean age of 65.2 yrs (SD 5.4). Individuals with evidence of intellectual deterioration or a history of stroke or brain injury were not included. All subjects gave informed consent.

### *Measures*

#### *Neuropsychological measures*

*Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1955).* All subjects were given a short form of the WAIS (Powell, 1979) comprising Vocabulary, Similarities, Comprehension, Block Design and Object Assembly subtests. All subjects were assessed once only on the WAIS. The patient group were assessed while on normal dopaminergic medication.

*Paced Auditory Serial Addition Task (PASAT) (Gronwall and Wrightson, 1981).* This task was intended as a measure of general attentional ability. It has been shown not to correlate either with general intelligence of arithmetic ability (Gronwall and Wrightson, 1981). Subjects listened to a recorded series of 30 random single digit numbers. Their task was to add the most recent number to the number immediately preceding it and to give the total. Subjects practised the task until they understood what was required. Two versions of the test were given. In the first, the numbers were presented at the rate of 1 every 4 s. In the second version, the rate was 1 number every 2 s. Subjects were given an error score for each condition, and a total score for the two conditions combined.

*Wisconsin Card Sorting Test (WCST) (Nelson, 1976).* This is a popular clinical measure of conceptual ability and behavioural regulation, and has previously been shown to be sensitive to frontal lobe damage (Drewe, 1974; Nelson, 1976). Measures were taken of number of categories sorted and the number of perseverative errors, nonperseverative errors and the percentage of perseverative errors.

*Visual-Visual Conditional Associative Learning Test.* This task required the learning of arbitrary associations between pairs of visual stimuli. Conditional associative learning tests were originally designed for animal experiments, where they were shown to be sensitive to damage to prefrontal cortex. Petrides (1985) adapted them for human use and confirmed the sensitivity of the tests to damage to prefrontal areas. The version of the test used in the present study was the same as that used by Canavan and Passingham (1985). It consisted of a set of cards bearing 6 nonmeaningful geometric designs, and 6 other cards each of a different colour. Each colour was arbitrarily paired with 1 of the 6 designs. The subjects were shown the coloured cards one at a time in a predetermined random sequence. For each colour, the subject had to point to the design with which they thought it was paired. For each choice, the subject was told whether or not it was correct. If the choice was wrong, the subject continued indicating designs until the correct pairing was made. The subject then proceeded to the next colour and continued until all 6 colours had been presented and correct pairings made. This constituted the first trial. A new design card was then presented bearing the same 6 designs but in different positions on the card. The colour cards were then presented one at a time in a new sequence This procedure was repeated 6 times, and the total number of errors recorded, as well as the number of errors per trial.

*Word Fluency Tasks.* Word fluency deficits have frequently been associated with damage to the frontal lobes (Milner, 1964; Borkowski *et al.*, 1967; Benton, 1968). A study by Newcombe (1969), however, casts some doubt upon the specific localizing value of category fluency tasks. She required subjects to generate words from both a single semantic category and from two alternating categories and found that impairment on both tasks was not specific to frontal lobe pathology. Despite this negative result, a version of Newcombe's fluency task was included in the present study. This was because of findings from other studies that alternation between conceptual categories is impaired in Parkinson's disease (Cools *et al.*, 1984; Flowers and Robertson, 1985). The alternating fluency task would permit a further measure of this ability, and permit study of the relationship between this task and other more specific 'frontal' tests. The single category version served as a control condition to assess speed of word production in the absence of alternation between conceptual categories. The first fluency test employed in the present study required the subjects to name as many exemplars of a single category (e.g., animals) as they could, in 1 min. The second required them to name alternately exemplars from two different categories (e.g., boys' names and fruit). Subjects' responses were recorded and errors noted. Subjects received a score of the total number of correct responses for each task.

*Subject-Ordered Pointing Tasks.* This was a series of three self-ordered tasks requiring the organization of a sequence of pointing responses. This class of task was originally designed to demonstrate deficits in monkeys after bilateral frontal lobe lesions (Pinto-Hamuy and Linck, 1965). The value of the test in demonstrating human frontal lobe pathology was shown by Petrides and Milner (1982). The version of the test used in the present study was in three parts, which differed only in the nature of the stimuli. One part used representational drawing, another abstract designs and the last, low imagery words. In each condition, the subject was presented with 12 cards in sequence, each bearing the same 12 stimuli arranged randomly on the card The subject's task was to point to a different stimulus on each card. The number of errors (i.e., pointing to a stimulus on more than one occasion) was recorded for each condition, and a total error score calculated.

### *Neurological measures*

Directly following each neuropsychological assessment, the severity of the signs and symptoms of each patient's Parkinson's disease was assessed using the King's College Hospital Parkinson's disease rating scale. Tremor, rigidity, akinesia and posture are rated, as well as gait, balance and autonomic signs. A high score (range 0–117) indicates increasing severity.

### *Assessment of subjective affect and arousal*

Immediately before administration of the neuropsychological tests, each subject completed a measure of subjective affect and arousal. This measure consisted of 16 100 mm analogue scales bearing pairs of adjectives such as 'happy–sad' and 'alert–drowsy' (Bond and Lader, 1974). The subject was required to indicate on the line joining each pair of adjectives the position which best described their current state. Three of the 16 scales were excluded because they were loaded heavily on motor status ('well-coordinated–clumsy', 'strong–feeble', 'tense–relaxed'). A total 'affect-arousal' score was computed for each subject, by taking the average response for the remaining scales. A high score indicated an adverse state. The same measure was used by Brown *et al.* (1984) and shown to be a useful predictor of cognitive function in patients off levodopa treatment.

## *Procedure*

All control subjects were tested on all measures. For the Parkinson's disease group, however, the number of subjects varied for individual neuropsychological tests (WAIS n = 16, PASAT n = 16, WCST n = 15, Conditional Learning, n = 16, Word Fluency n = 15, Subject-Ordered Pointing n = 10).

In order to minimize practice effects, two equivalent forms (A and B) were made of the PASAT, and the Conditional Learning, Word Fluency and Subject-Ordered Pointing Tests.

The 16 patients were randomly assigned to two groups to determine whether they were initially tested on or off medication. Within each subgroup, half were tested first with version A of alternate form tasks, and half with version B. All patients were then assessed after an interval of approximately one week, in the opposite treatment condition and on the alternative form of each test. For the 'off' testing, patients ceased all antiparkinsonian medication a minimum of 16 h before assessment. Patients were assessed in their own homes.

The 16 control subjects were randomly assigned to two groups, receiving first either version A or version B of the alternate form tests, and the second form on the subsequent occasion. The intertest interval was one week. Test administration and scoring was the same as for the patient group. Controls received all measures except for the Parkinson's disease rating.

## RESULTS

There was no significant difference between the mean ages of the patient and control groups (t = 0.38, df = 29.6, $P = 0.70$). The difference in sex ratios was not significant ($\chi^2 = 2.1$, df = 1, $P > 0.05$). Verbal IQ did not differ (t = 1.31, df = 30, $P = 0.20$) but a significant difference in Performance IQ was found between the two groups (t = 2.28, df = 30, $P < 0.05$). Comparison of individual subtests, however, revealed no significant differences between the groups (Table 1).

TABLE 1 WAIS IQ DATA PARKINSONIAN AND CONTROL GROUPS

| | *Parkinsonian group*<br>*Mean* (*SD*) | *Control group*<br>*Mean* (*SD*) |
|---|---|---|
| Verbal IQ | 126 5 (18 6) | 133 8 (11.8) |
| Performance IQ | 105 4 (12.4)* | 117 6 (17 5) |
| Vocabulary | 13.7 (2 9) | 14 9 (2 3) |
| Comprehension | 14 9 (4 1) | 16 2 (2.8) |
| Similarities | 11 8 (3.1) | 12 6 (2.0) |
| Block Design | 8 6 (2 3) | 10 6 (3 5) |
| Object Assembly | 6.9 (2 6) | 8 4 (3 4) |

*$P < 0$ 05 Student's t test

### *Control subjects*

The control group served three functions: first to assess the equivalence of the alternate test forms, secondly to evaluate practice effects, and thirdly, to serve as a comparison group for the Parkinson's disease group.

*Comparison of alternate test forms.* Comparison of the two forms of each test were made using paired t tests. No significant difference was found between forms A and B of any of the tests apart from the single category condition of the verbal fluency test (t = 2.80, df = 7, $P < 0.05$). With the exception of this test, it could be assumed that the two forms of each test were of equivalent difficulty.

*Practice effects.* Comparing scores across the two occasions revealed two significant practice effects: improved performance on the slower version of the PASAT (t = 2.33, df = 7, $P < 0.05$) and a decrease in the number of perseverative errors on the WCST (t = 2.73, df = 7, $P < 0.05$).

The results from the control group suggested minimal practice effects and equivalence between alternate forms of the tests. Any deviations from this should not affect either between group comparisons or 'on–off' comparisons in the Parkinson's disease group, owing to the balanced nature of the design of the study. The mean scores for the control group and for Parkinson's disease group ('on' and 'off') are shown in Table 2.

TABLE 2 MEAN VALUES AND SDs FOR ALL TEST SCORES IN PARKINSON'S DISEASE (PD) PATIENTS AND CONTROL SUBJECTS

| *Test* | *PD ('on')* | *PD ('off')* | *Controls* |
|---|---|---|---|
| Subjective Affect/Arousal | 34.06 (13.1) | 50.54 (7.6) | 28.59 (13.4) |
| PASAT (errors) | | | |
| Slow | 7.33 (5.7) | 8.13 (6.5) | 4.63 (5.9) |
| Fast | 13.73 (4.6) | 15.20 (5.8) | 11.84 (5.4) |
| WCST | | | |
| Categories | 3.56 (2.2) | 3.66 (2.0) | 5.19 (1.1) |
| Perseverative errors | 5.62 (5.9) | 4.93 (6.3) | 1.40 (1.6) |
| Nonperseverative errors | 12.37 (8.1) | 12.60 (7.5) | 6.81 (5.0) |
| % perseverative errors | 24.53 (19.4) | 21.64 (16.7) | 11.19 (13.5) |
| Conditional Learning | | | |
| Total errors | 58.56 (20.3) | 52.10 (25.2) | 40.60 (15.6) |
| Word Fluency | | | |
| Single | 23.18 (11.2) | 20.60 (7.6) | 24.18 (7.4) |
| Alternate | 16.25 (2.8) | 14.53 (3.7) | 19.43 (3.1) |
| Subject-Ordered Pointing (errors) | | | |
| Representational pictures | 1.41 (1.1) | 1.27 (0.8) | 0.84 (0.6) |
| Abstract pictures | 3.08 (1.5) | 2.45 (1.9) | 2.22 (0.6) |
| Low imagery words | 1.58 (1.1) | 1.55 (1.1) | 1.19 (0.9) |

### *Comparison between Parkinson's disease group 'on' and 'off' levodopa*

While the study employed a balanced design, the possibility existed that patients tested 'on' first might benefit differently on subsequent testing to patients tested 'off' first. To check for the presence of such asymmetric transfer effects, patients tested in the order 'on–off' were compared with patients tested in the order 'off–on'. No significant effect of order of testing was found for any measure. These two groups were therefore combined for all subsequent analyses.

Comparisons of test performance 'on' and 'off' medication, were carried out by repeated measures analysis of variance using the MANOVA procedure of SPSS-X (SPSS Inc., Staff 1983). Results of the analyses are shown in Table 3. For none of the tests was the effect of medication (on vs off) significant. Comparison of affect-arousal scores revealed that the patients reported a more adverse state when 'off' than when 'on' (F(df) = 28.80(1,14), $P < 0.001$). Because of the possible influence of mood and arousal on test performance the on–off comparisons were

TABLE 3 MANOVA RESULTS FOR PARKINSON'S DISEASE PATIENTS 'ON' VERSUS 'OFF' LEVODOPA TREATMENT

| *Test* | *Effect* | *F (df)* | *P* |
|---|---|---|---|
| PASAT | On/off | 0.54 (1,13) | 0.48 |
| | Slow/fast | 43.45 (1,13) | <0.01* |
| | On/off × Slow/fast | 0.35 (1,13) | 0.57 |
| WCST | | | |
| Categories | On/off | 0.45 (1,13) | 0.51 |
| Perseverative errors | On/off | 0.61 (1,13) | 0.45 |
| Nonperseverative errors | On/off | 0.85 (1,13) | 0.85 |
| % perseverative errors | On/off | 0.68 (1,12) | 0.43 |
| Conditional Learning | On/off | 1.80 (1,14) | 0.20 |
| | Trial (1–6) | 4.26 (5,10) | <0.05* |
| | On/off × Trial | 0.35 (1,14) | 0.87 |
| Word Fluency | On/off | 1.12 (1,13) | 0.31 |
| | Single/alternate | 16.35 (1,13) | <0.01* |
| | On/off × Single/alternate | 0.01 (1,13) | 0.94 |
| Subject-Ordered Pointing | On/off | 2.00 (1,9) | 0.19 |
| | Material | 4.08 (2,8) | 0.06 |
| | On/off × Material | 3.28 (1,9) | 0.09 |

* Significant effect ($P < 0.05$).

repeated with affect-arousal score a covariate. Its influence, however, was not significant for any of the tests.

Significant task effects were found for two of the tests, PASAT and word fluency; that is, performance on the fast version of the PASAT was worse than performance on the slow version, and fewer words were generated on the alternating category condition than on the single category condition of the fluency tests. However, there were no significant interactions between task effects and 'on' versus 'off' states.

### *Comparison between Parkinson's disease group 'on' and control group*

Results of the analyses are shown in Table 4. No significant difference was found between the affect-arousal scores of the patients when 'on' medication, and the control group (F(df) = 1.36(1,30), $P = 0.25$), and so this measure was not used as a covariate in subsequent analyses.

Results from the MANOVAs are shown in Table 4. The patients performed significantly worse on all indices of the WCST. They also performed worse on the conditional learning test and the subject-ordered pointing. In contrast, no significant difference was found for performance on the PASAT or the word fluency tasks.

Fig. 1 shows the pattern of errors per trial on the conditional learning test. While the Parkinson's disease group made more errors overall, there was no significant group by trial interaction, suggesting both groups improved equally across the 6 trials. For the subject-ordered pointing test, patients again made more errors overall, but with no significant interaction between groups and errors on the three types of material in the test.

TABLE 4 MANOVA RESULTS FOR PARKINSON'S DISEASE (PD) 'ON' AND 'OFF' LEVODOPA TREATMENT COMPARED WITH CONTROL SUBJECTS

| | | *PD ('on') vs Control* | | *PD ('off') vs Control* | |
|---|---|---|---|---|---|
| *Test* | *Effect* | *F (df)* | *P* | *F (df)* | *P* |
| PASAT | Group | 1.58 (1,29) | 0.22 | 2.89 (1,29) | 0.10 |
| | Slow/fast | 97.29 (1,29) | <0.01* | 114.33 (1,29) | <0.01* |
| | Group × Slow/fast | 0.35 (1,29) | 0.56 | 0.01 (1,29) | 0.91 |
| WCST | | | | | |
| Categories | Group | 6.78 (1,30) | <0.01* | 6.76 (1,29) | <0.01* |
| Perseverative errors | Group | 7.58 (1,30) | <0.01* | 4.69 (1,29) | <0.05* |
| Nonperseverative errors | Group | 5.45 (1,30) | <0.05* | 6.41 (1,29) | <0.05* |
| % perseverative errors | Group | 4,89 (1,30) | <0.05* | 3.45 (1,28) | 0.07 |
| Conditional Learning | Group | 7.54 (1,30) | <0.01* | 1.81 (1,30) | 0.19 |
| | Trial (1–6) | 5.08 (5,26) | <0.01* | 3.31 (5,26) | 0.02 |
| | Group × Trial | 0.43 (5,26) | 0.83 | 0.22 (5,26) | 0.95 |
| Word Fluency | Group | 0.85 (1,30) | 0.36 | 6.00 (1,29) | <0.05* |
| | Single/alternate | 15.94 (1,30) | <0.01* | 9.05 (1,29) | <0.01* |
| | Group × Single/alternate | 0.31 (1,30) | 0.58 | 6.86 (1,29) | <0.01* |
| Subject-Ordered Pointing | Group | 8.16 (1,26) | <0.01* | 1.18 (1,25) | 0.29 |
| | Material | 15.30 (2,25) | <0.01* | 16.14 (2,24) | <0.01* |
| | Group × Material | 0.34 (2,25) | 0.71 | 0.09 (2,24) | 0.92 |

*Significant effect. For Conditional Learning (Trial and Group × Trial effects), and Self-Ordered Pointing (Material and Group × Material effects), F = approximate F. For remaining tests, F = univariate F.

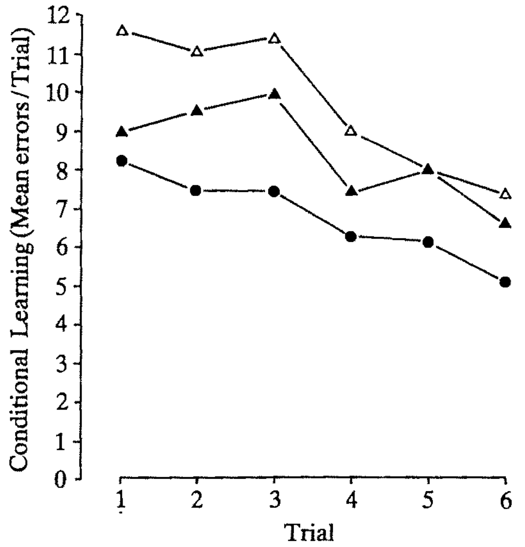

FIG 1 Mean errors per trial on the Conditional Learning task for the Parkinson's disease group 'on' and 'off' medication, and for the control group. Parkinson's disease group 'on' medication (△—△), Parkinson's disease group 'off' medication (▲—▲); Control group (●—●)

### *Comparison between Parkinson's disease group 'off' and control group*

Results of the analyses are shown in Table 4. For the WCST, the pattern was very similar to that found when the patients were 'on' medication, with the exception that the comparison of percentage perseverative errors just failed to reach significance. In contrast to their performance when 'on' medication, the patients when 'off' were no worse than controls on the conditional learning task or the subject-ordered pointing. Verbal fluency, however, which was unimpaired when 'on' was significantly worse in the patients when 'off' levodopa. In addition to this main effect between the groups, there was a significant interaction between group and the single-versus-alternate fluency conditions. Examination of the means revealed that the patients when 'off' showed increased impairment on the alternating fluency condition. This finding can be seen also in figs 2c and 2d, where the scores of individual subjects are shown.

Patients when 'off' reported a significantly worse affect-arousal state than controls (F(df) = 19.90(1,30), $P < 0.001$). Because of this, all of the above analyses were repeated with affect-arousal as a covariate. As with the 'on' versus 'off' comparison,

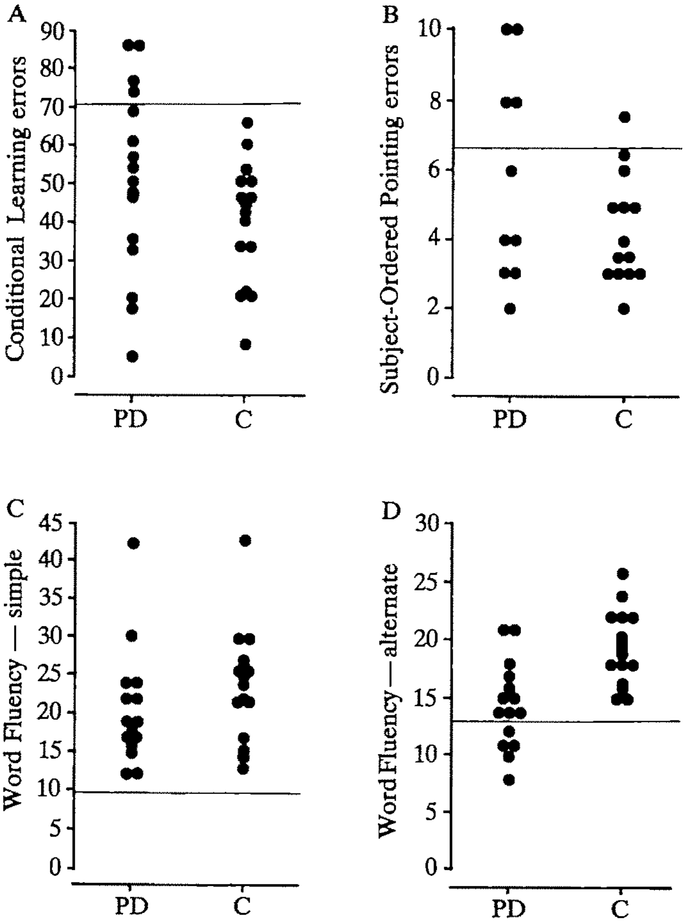

FIG. 2. Performance of individual subjects in the control group (C) and Parkinson's disease group (PD) 'off' medication, on A, Conditional Learning Test, B, Subject-Ordered Pointing, C, Word Fluency (simple condition) and D, Word Fluency (alternate condition).

including the covariate did not substantively alter the pattern of significant and nonsignificant results.

### *Associations between measures in the patients with Parkinson's disease*

*Associations between disease factors and neuropsychological measures.* Duration of illness was not significantly associated with any of the neuropsychological test measures, either 'on' or 'off' medication. Symptom severity as measured by the Parkinson's disease rating scale, was related only to subject-ordered pointing error when 'on' levodopa. Levodopa dose, however, was associated with some, but not all neuropsychological tests when measured on medication. The strongest association was a positive correlation ($r=0.62$, $P<0.01$) between dose and the number of errors on the conditional learning test, that is, the higher the dose the greater the number of errors. To assess whether this relationship was being mediated by factors such as age or duration of illness, partial correlations were calculated.

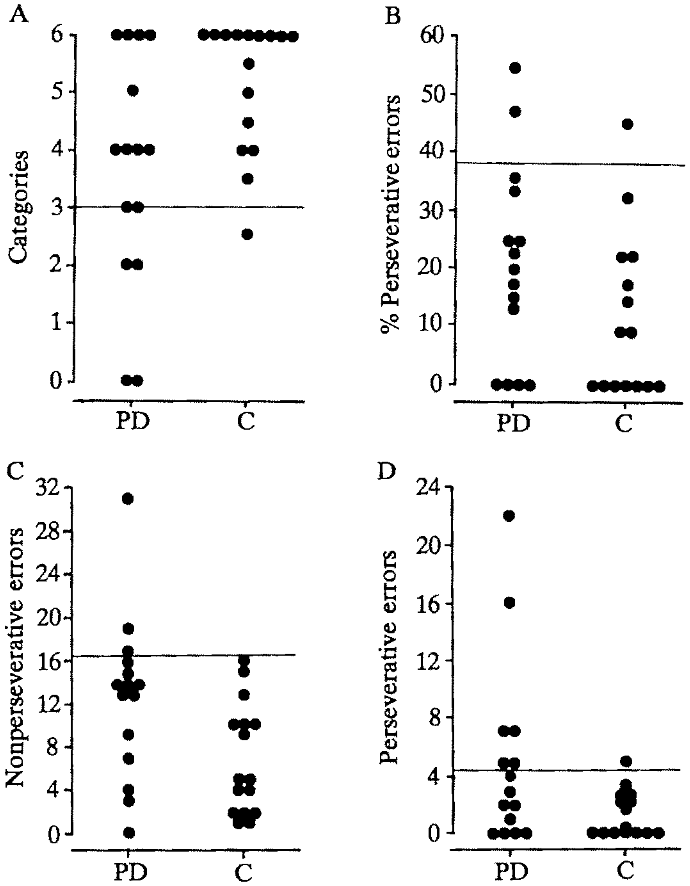

FIG 3. Performance of individual subjects in the control group (C) and Parkinson's disease group (PD) 'off' medication, on the Wisconsin Card Sorting Test. A, number of categories; B, % perseverative errors, C, number of nonperseverative errors and D, number of perseverative errors

Controlling for these other factors, however, had little impact on the strength of the association between levodopa dose and conditional learning errors ($r=0.57$, $P<0.05$). Levodopa dose was also significantly positively associated with the number of nonperseverative errors on the WCST ($r=0.46$, $P<0.05$), and the association with number of categories just failed to reach significance ($r=0.41$, $P=0.06$) (fig. 3). These two correlations should not be considered as independent, however, as WCST categories and number of nonperseverative errors were themselves highly correlated ($r=-0.93$, $P<0.001$). Thus performance on the conditional learning test and the tendency to make nonperseverative errors on the WCST (and possibly therefore sort fewer categories), seem to be adversely affected by increasing doses of levodopa. It is unlikely that the cause of this is a generalized attention deficit, as levodopa dose was only weakly associated with performance on the PASAT ($r=0.16$, $P>0.05$). Levodopa dose was also unrelated to the other neuropsychological measures: WCST perseverative errors ($r=0.28$, $P>0.05$), WCST percentage perseverative errors ($r=0.18$, $P>0.05$), Subject-Ordered Pointing errors ($r=-0.06$, $P>0.05$), Word Fluency (single category) ($r=-0.02$, $P>0.05$) or Word Fluency (alternate category) ($r=0.17$, $P>0.05$).

*Association between neuropsychological measures, both 'on' and 'off' levodopa.* Table 5 shows the intertest correlations for the patients both 'on' levodopa (upper right-hand triangle) and 'off' levodopa (lower left-hand triangle). Taking first the patients 'off' medication, who represent the true parkinsonian state most closely, the various indices of performance on the WCST are tightly clustered with the exception of the association between nonperseverative errors and percentage perseverative errors. Performance on the WCST, again with the exception of nonperseverative errors, was also closely associated with performance on the subject-ordered pointing tests (although the association with WCST categories just failed

TABLE 5. CORRELATION MATRICES BETWEEN 'FRONTAL' TEST MEASURES FOR THE PARKINSON'S DISEASE GROUP 'ON' AND 'OFF' LEVODOPA**

| | *WCST (Cats)* | *WCST (NPE)* | *WCST (PE)* | *WCST (%PE)* | *Conditional Learning errors* | *Subject-Ordered Pointing errors* | *Verbal Fluency (single)* | *Verbal Fluency (alternate)* |
|---|---|---|---|---|---|---|---|---|
| WCST (Cats) | | −0.93* | −0.69* | −0.34 | −0.45* | 0.05 | 0.27 | −0.06 |
| WCST (NPE) | −0.88* | | 0.52* | 0.23 | 0.46* | 0.01 | −0.17 | 0.08 |
| WCST (PE) | −0.75* | 0.49* | | 0.80 | 0.56* | 0.03 | −0.16 | −0.25 |
| WCST (%PE) | −0.62* | 0.30 | 0.90* | | 0.42 | 0.04 | −0.21 | −0.29 |
| Conditional Learning errors | −0.49* | 0.39 | 0.17 | 0.13 | | 0.46 | −0.15 | −0.37 |
| Subject-Ordered Pointing errors | −0.47 | 0.35 | 0.56* | 0.56* | 0.21 | | 0.13 | −0.46 |
| Verbal Fluency (single) | 0.12 | 0.05 | −0.24 | −0.10 | −0.56* | −0.19 | | 0.35 |
| Verbal Fluency (alternate) | 0.48* | −0.43 | −0.62* | −0.52* | −0.46* | 0.17 | 0.48* | |

* $P<0.05$. ** The upper right half matrix represents the correlations between measures when the patients were on medication The lower left half matrix represents the correlations between measures when the patients were off medication WCST = Wisconsin Card Sorting Test, (Cat) = categories; (NPE) = nonperseverative errors, (PE) = perseverative errors, (%PE) = percentage perseverative errors

to reach significance), and on the alternating version of the Verbal Fluency Test. In contrast, WCST performance was unrelated to the single category condition of the Verbal Fluency Test. The relationship between WCST and conditional learning test performances was more variable. Conditional learning errors were associated with number of categories and nonperseverative errors on the WCST (although the latter association just failed to reach significance) but not with either of the indices of perseverative errors. The intercorrelations between the tests other than the WCST were also variable. Conditional learning but not subject-ordered pointing was associated with both measures of verbal fluency, while conditional learning and subject-ordered pointing were themselves unrelated.

A less consistent pattern of associations was found when the patients were 'on' levodopa. Again the indices of performance on the WCST tended to cluster, and in this instance, all indices were significantly or nearly significantly associated with performance on the conditional learning test. With the exception of this association between the WCST and the Conditional Learning Test, no other consistent pattern emerges. Subject-ordered pointing errors tended to be associated with conditional learning errors and performance on the alternating word fluency condition, although because of the reduced sample size that received the subject-ordered pointing test, these correlations just failed to reach significance.

## DISCUSSION

This study was planned to assess, in Parkinson's disease, the influence of dopamine stimulation and depletion on cognitive functions generally associated with the frontal lobe. If cognitive function was found to change between the medicated and nonmedicated states, it was important to assess the influence of factors such as changes in attention, arousal and mood between the two states. Girotti *et al.* (1986) found an apparent worsening in attention in their patient group when off medication. Their test, however, was based on psychomotor speed and was therefore probably unsuitable for such a patient group without appropriate control conditions. In the present study, the PASAT was chosen, a nonmanual attentional task without a speed component. Using this test, with the present patient group, no evidence was found of a significant attentional deficit, either on or off levodopa. In contrast, a global measure of subjectively rated affect and arousal revealed an adverse state in the patients when off medication, compared both with their own ratings when on levodopa, and with the control group. This result is the same as that previously reported by Brown *et al.* (1984). In the present instance, however, the adverse affect-arousal state did not appear to be an important determinant of cognitive function. Thus changes in attention, arousal and mood cannot be offered as major explanations for any of the changes seen in cognitive function in the Parkinson's disease group.

The results from the present study raise two separate issues which need to be discussed. The first is the effect of the underlying pathology and neurochemical disturbances of Parkinson's disease on the cognitive functions tested. This can best be judged by considering patients not on dopaminergic replacement medication. The second is the impact of dopamine stimulation on those cognitive functions.

When off medication, the patients were impaired on some but not all of the neuropsychological measures when compared with normal age matched controls. While all the tests were chosen on the a priori basis that they were assessing functions of the prefrontal region, it seems clear that considerable heterogeneity exists within those functions. The patients were impaired on the various indices of performance of the WCST (although the deficit in percentage perseverative errors just failed to reach statistical significance), as well as on the word fluency tests. In contrast, they were not significantly impaired on either the conditional learning test or the subject-ordered pointing.

Two main possibilities exist to explain this dissociation. The first is that not all the tests are really 'frontal'. The second is that the tests tap different aspects of frontal function and only certain aspects are compromised in patients when off dopaminergic medication. The first possibility can probably be excluded because of the careful work which has gone into evaluating the impact of frontal lobe lesions on conditional learning and subject-ordered pointing, both in man and monkeys. The alternative explanation, namely that different tests tap different frontal lobe functions, is in agreement with the results of many years of study of frontal lobe function in man and animals (*see* Stuss and Benson, 1986, for a review). The frontal cortex is not homogeneous, either anatomically or functionally, with distinctions drawn between regions such as medial, orbital and dorsolateral frontal cortex. Agreement, however, as to the specialized functions of these different areas has not yet been reached, at least in man. Stuss and Benson (1986) concluded that the evidence for differences in function must be evaluated with 'caution and deliberation'. The lack of agreement can be judged by the attempts to localize the crucial lesion site for impairment on the WCST. Milner (1964) found impairment to be maximal following dorsolateral frontal lesions, particularly to the area outside the inferior frontal cortex. Stuss *et al.* (1982, 1983), however, found impairment following orbitofrontal leucotomy lesions, while Drewe (1974) suggested that the crucial lesion was medial, not dorsolateral. In monkeys, Mishkin (1964) found greater impairment on an analogous task following orbital than dorsolateral lesions.

Wherever the critical lesion site, if indeed there is one, performance on the WCST seems to be impaired in patients with Parkinson's disease when off levodopa. In addition, the patients were impaired on the verbal fluency tasks. It might be argued that this latter deficit is attributable, in part, to slowing in the generation of verbal responses independent of cognitive impairment. This seems unlikely, however, as verbal fluency, for the single category condition at least, was *positively* correlated with parkinsonian severity ($r = 0.41$), that is, the more severe the Parkinson's disease, the more words were produced in 1 min. Analysis of the results for the single and alternating category conditions revealed a significant group by condition interaction. It can be seen from figs 2C and D, which show the scores of individual patients and controls, that the performance of all the patients on the single category condition lay within the normal range. In contrast, their performance on the alternating category condition shows a clear group deficit, with one-third of the patients being outside the normal range. As both verbal fluency conditions had identical motor response components, the impairment in the alternating condition can safely be attributed to cognitive factors. The key component of the task was the ability to alternate rapidly between two conceptual categories. It is of interest therefore, that performance on the alternating task was associated with the WCST, particularly the measures of perseveration (Table 5). In contrast the WCST and single category fluency were unrelated.

If performance on the WCST and alternating fluency task are related and both are impaired in patients when off levodopa, what of the subject-ordered pointing and conditional learning tasks? Subject-ordered pointing errors were associated mainly with perseverative errors on the WCST, while conditional learning errors were associated mainly with categories and nonperseverative errors. Despite these associations, analysis of group means revealed that in neither case were the patients impaired when compared with normal controls. For subject-ordered pointing, this may be in part due to the small sample size receiving this test (n = 10). Fig. 2B shows that 40% of patients scored outside the normal range. With a larger sample, therefore, a significant impairment on this task might be revealed. With conditional learning the presence of a deficit is less clear. Fig. 2A shows that only 25% of patients had abnormal scores, the large majority scoring within the normal range. Thus whatever the cause of the deficit leading to impairment on the WCST, the alternating word fluency condition, and possibly on the subject-ordered pointing, it seems to have little influence in the majority of patients on performance of the conditional learning test.

It might be concluded from this that the former tests, but not the latter, were dependent on dopamine. In order to conclude this, however, it is necessary to show not only that performance is impaired when dopamine stimulation is withdrawn, but that performance is normalized by reintroduction of dopamine. Comparison of patients on medication with normal controls revealed that performance on the verbal fluency tests was no longer significantly impaired. Dopamine replacement, therefore, seems to have normalized performance, lending support to the idea that performance on this task was dependent upon brain dopamine levels, possibly in the caudate. In direct contrast, performance on the subject-ordered pointing and conditional learning tests, which were largely unimpaired when the patients were 'off' levodopa, were significantly impaired compared with normal controls when medication was reintroduced. We therefore have the unexpected situation where a drug, which leads to a marked improvement in motor function, has much more variable influence on cognitive function, improving some, but leading to a deterioration in others.

Adverse effects of levodopa are not uncommon. In extreme cases patients become confused, hallucinatory or psychotic (Parkes, 1981). Such reactions seem particularly marked in patients with dementia (Sacks *et al.*, 1972). There is some indication, however, that levodopa may lead to more subtle changes. Barbeau (1971) described '... a gradual decrease in attention span ... and occasionally loss of memory for recent events.... In some patients, modifications in social behaviour were also observed which are best described as frontal-lobe-like insouciance.' It is sometimes difficult, when the changes are gradual, to distinguish between medication effects and the natural progression of the disease. In the present instance the changes seemed to be the result of acute modifications of brain dopamine levels. By what mechanisms might levodopa lead to a disruption in cognitive function? It has long been known that the dose-response curves in normal animals and humans for drugs such as amphetamine are an inverted U-shape, with optimum performance occurring with intermediate doses (Robbins and Sahakian, 1983). In Parkinson's disease, there is greater dopamine depletion in the motor putamen than in the caudate or prefrontal cortex. Levodopa doses necessary to remedy the dopamine lack in the putamen may 'overdose' any area where dopamine regions are relatively intact, namely, the prefrontal cortex and probably the caudate in a significant proportion of patients. This overdosage hypothesis is supported by the positive association between conditional learning errors and levodopa dose. This relationship was not found for the subject-ordered pointing task, although, as noted above, the results from this test seem rather ambiguous owing to the reduced sample size.

If overdosage does occur and lead to disruption of function, then it suggests that performance on the conditional learning test and possibly the subject-ordered pointing test are crucially dependent upon different regions of prefrontal cortex to those involved with the alternating verbal fluency task, but that in both cases dopamine levels are an important determinant of function. We can call these regions A and B, with dopamine levels being depleted more in one than in the other. To go further and tie them into specific neuronal systems is premature, given our inadequate current knowledge of dopamine levels in different regions of cortex and caudate in living patients. That leaves the WCST. In the present study, performance on the WCST was impaired both on and off levodopa. This suggests two possibilities. Either the impairment is independent of brain dopamine levels, or the test is sensitive to disruption from a wide variety of brain regions. The clinicopathological correlates discussed earlier suggested that there was no single critical frontal lesion site for producing WCST impairment. It still remains to be determined whether dopamine levels are an important determinant of WCST performance.

The results from the present study have shown a double dissociation of performance on two groups of tests in the same patient group under two conditions of dopamine stimulation. The value of this double dissociation is diminished by the fact that it was not predicted, and replication or further empirical investigation is vital. The post hoc interpretation of the results may be accepted as providing a reasonable working model. It is inevitably an oversimplification, however, to think of two independent neuronal systems and two independent sets of neuropsychological tests. More likely is that all tests are influenced by any neuronal disruption within the frontal systems, but that certain tests may be *relatively* more sensitive to disruption in one of the two systems. The actual pattern of deficits seen on and off medication will depend upon the levels of dopamine in the systems. If both are depleted then a more generalized deficit might be expected when off medication with improvement when levodopa is administered. If both are relatively normal, then performance on all 'frontal' tests might be impaired by medication. Finally, an imbalance in dopamine levels will lead to some functions improving and some deteriorating. In a patient sample such as that used in the present study, all such cases probably existed. This heterogeneity may explain why overall there was no significant difference when comparing patients on and off levodopa, and that impairment only became evident when making the more extreme comparison with normal controls.

It is perhaps wise to conclude on a note of caution. The present study set out to test two relatively simple hypotheses, first that patients with Parkinson's disease are impaired on tests thought to depend upon the functional integrity of the prefrontal cortex and associated neuronal circuits and secondly, that any frontal deficits would be associated with the status of dopamine depletion or stimulation. The results confirmed both hypotheses, but the picture which emerged suggests that the relationship between dopamine and cognitive function in the frontal system is more complex than formerly believed. We have used information from postmortem and in vivo studies to try and build a framework for interpreting the findings. The interpretation is, however, speculative. It is clear that studies are required in which patients are classified on an a priori basis according to their levels of dopamine depletion in areas such as the caudate and prefrontal cortex. PET scanning may permit such classification. These various patient groups could then be tested under various conditions of levodopa stimulation and depletion to plot more accurately the dose-response curves relating levodopa to cognitive function.

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# INTERNAL VERSUS EXTERNAL CUES AND THE CONTROL OF ATTENTION IN PARKINSON'S DISEASE

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## SUMMARY

In recent years, several attempts have been made to characterize the nature of the cognitive deficits shown by patients with Parkinson's disease. It has been suggested variously that they have difficulty in switching cognitive set, in performing effortful (or controlled) as opposed to automatic tasks, or that their impairment is found in tasks which maximize the amount of 'self-directed task specific planning'. It is proposed that this latter distinction may be reformulated in terms of the degree of internal versus external attentional control which is required by the task. An experiment is described which attempted to manipulate this parameter. A version of the Stroop colour-word test was used, in which the words 'red' and 'green' were presented in the complementary coloured 'ink'. Subjects responded either to the colour of the ink in which the word was written or the colour named by the word. The relevant attribute changed at intervals during the course of the experiment. In one condition, the relevant stimulus attribute was cued before each trial. In another condition, subjects had to remember which attribute was currently relevant Results revealed that patients with Parkinson's disease were impaired mainly on the second version of the task which required internal attentional control. The results are discussed in relation to the models of Working Memory (Baddeley, 1986), and attentional control (Norman and Shallice, 1980). Exploration of these models leads to the formulation of a theory in which the crucial determinant of cognitive impairment in Parkinson's disease is reduced resources in the Supervisory Attentional System. Provided the demands of the task are within the patient's available attentional resources the patient may not show any deficit. If, however, the attentional demands exceed available resources, as in tasks which depend upon internal cues, then deficits will be observed.

## INTRODUCTION

Patients with Parkinson's disease, as a group, are impaired on a wide range of tests of cognitive function. Contemporary concepts have focused on the similarity between the deficits shown by patients with Parkinson's disease, and those shown by patients with a lesion of the prefrontal cortex (*see* Brown and Marsden, 1987, for a review).

One theory that attempts to explain some of the range of cognitive deficits in

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Parkinson's disease as due to a loss of flexibility in information processing, has parallels with theories of frontal cortical function. A number of recent investigators have proposed that patients with Parkinson's disease have deficits in alternating between two or more tasks or ways of processing the same stimulus configuration (Bowen, 1976; Lees and Smith, 1983; Cools *et al.*, 1984). Cools *et al.* studied a range of cognitive and motor tasks, and concluded that patients with Parkinson's disease have a generalized deficit in 'shifting-aptitude'. In addition there is evidence to suggest that patients with Parkinson's disease also have difficulty in 'maintaining set' once they have 'shifted' (Flowers and Robertson, 1985).

For such a theory to be of value in explaining more than just a narrow range of deficits, it is necessary to demonstrate that the impairment is a general one, found with any cognitive task. Brown and Marsden (1988) using a task described previously (Brown and Marsden, 1986), assessed a group of patients with Parkinson's disease on a test that required them to switch, at intervals, between two alternate modes of stimulus processing. In one mode they were required to make a simple left-right discrimination of a visual stimulus. In the second they had to rotate the stimulus mentally by 180 deg before they could make the left-right discrimination. Subjects received alternating blocks of the two tasks, each block consisting of 10 trials. Both patients and controls showed an increase in reaction time (RT) when required to alternate, followed by a reduction in RT within each block as it progressed. While the patients were slower overall, they showed no differential slowing compared with controls when required to alternate, nor did they show any evidence of difficulty in maintaining set following the shift. Thus while the task elicited the components of shifting, acquisition and maintenance of a cognitive set, the patients with Parkinson's disease were unimpaired on these aspects of task performance. In contrast the same group of patients were impaired, on average, in all aspects of performance on the Wisconsin Card Sorting Test (WCST) (Nelson, 1976). This implies that the deficit suggested by Cools *et al.* (1984) is not generalizable to all tasks, even in the same patient group.

A second concept which seeks to explain a range of cognitive deficits in Parkinson's disease has been suggested by Weingartner *et al.* (1984). This theory, based on that of Shiffrin and Schneider (1977) makes a distinction between tasks involving 'effort-demanding' (also called 'controlled') cognitive processing (such as memory recall), and tasks involving 'automatic' processing such as recognition. Weingartner *et al.* suggested that patients with Parkinson's disease are differentially impaired on effort-demanding tasks. However, the effort-demanding/automatic distinction is of limited heuristic value without a means of defining tests a priori as effortful or automatic. Furthermore, studies which have manipulated levels of difficulty within a task (and therefore presumably the effort required), have failed to show any consistent differential effect of task difficulty/effort in Parkinson's disease (Wilson *et al.*, 1980; Rafal *et al.*, 1984; Brown and Marsden, 1986). Therefore the 'effort' theory, as it stands, is of uncertain heuristic value.

Taylor *et al.* (1986) proposed another theory with similarities to that of Weingartner *et al.* They administered a range of clinical neuropsychological tests to patients with Parkinson's disease, and found them to be impaired on the free recall of word lists, and WCST and a delayed spatial recognition test. The authors proposed that these tests have the common feature of requiring 'self-directed task specific planning'. In contrast, the same patients were unimpaired on tasks such as recognition memory, paired associate learning and various tests of visuospatial function, all of which, it was argued, provide a degree of external stimulus control. Unfortunately, the subjects were also unimpaired on a number of other tasks which might also be thought to rely to a large degree on self-directed planning, such as verbal fluency, the alternating condition of the Trial Making Test (Halstead, 1947), and the Money Map Test (Money, 1965). To account for this, the authors proposed that the tests on which the patients were impaired were those which 'maximized the need for self-directed planning'. Unfortunately, with standard clinical tests, it is often difficult to define, a priori, where along the continuum of external stimulus-directed and internal self-directed, a particular test lies, just as it is difficult to define 'effort'. Thus, while the results of Taylor *et al.* (1986) offer some support for their theory, they cannot be considered as unequivocal proof.

This theory, however, may explain the failure of Brown and Marsden (1988) to find any deficit in their patients on the RT task that they used, while the same group were impaired on the WCST. One difference between the WCST, on which patients with Parkinson's disease performed poorly (as a group), and the RT task employed by Brown and Marsden lay in the locus of attentional control. In the WCST, each stimulus has three attributes: colour, shape and number. In each trial there is nothing in the stimulus itself to indicate which of the three attributes is currently relevant. The subject must therefore focus attention on one attribute by means of some form of self-directed or 'internal' control. In contrast, in the RT task used by Brown and Marsden, each stimulus configuration contained an explicit (i.e., external) cue indicating how the stimulus was to be processed. Thus, to reformulate Taylor's model, patients with Parkinson's disease might be impaired in the use of internal cues for the control of attention, and it is only in tasks which require the use of such internal cues that they show deficits.

Clinical neuropsychological tests frequently have the disadvantage of being complex conceptually. While this may not interfere with their clinical utility, it may make them unsuitable for experimental studies where accurate control of individual task parameters if necessary (Brown and Marsden, 1987). The aim of the present study was to assess the value of the internal-external distinction by assessing the performance of a group of patients with Parkinson's disease on two forms of the same task. All parameters were held constant except that one version required internal attentional control, while in the other external cues were provided.

An adaptation of the Stroop colour-word test (Stroop, 1935) was used. This involves the presenting of colour-words such as 'red' or 'green' in a contrasting coloured ink. The Stroop test is normally administered either by asking the subject to sort cards bearing the stimuli, or to read out or name verbally the colour-word or the colour of the ink. Although results vary depending upon the paradigm used, almost all studies show clear effects of interference when subjects have to name/sort stimuli according to the colour of the ink, when there is a competing word meaning. This is the standard Stroop phenomenon (Stroop, 1935). Interference of the 'ink' with the word meaning, the 'inverse Stroop phenomenon', is less reliably demonstrated, and when found it is usually less marked than the standard Stroop effect.

As well as evaluating the significance of internal versus external cues in attentional control, the present study permitted the investigation of two other issues. First, it provided a further study of the phenomenon of 'cognitive set' in Parkinson's disease and its relationship to the question of locus of attentional control of the task. Secondly, it allowed an assessment of the sensitivity of patient's with Parkinson's disease to Stroop-type interference. This latter question is of some interest as it has been found that performance on the Stroop task is influenced by cortical lesions, particularly of the frontal lobes (Perret, 1974).

## METHODS

### *Subjects*

Sixteen patients with idiopathic Parkinson's disease served as the experimental group. All were currently on stable dopaminergic medication. Subjects with a history of stroke, head injury or neurosurgical operation (including thalamotomy) were excluded, as were patients with clinical evidence of dementia. Details of the 16 patients are shown in Table 1. Sixteen control subjects were chosen from a volunteer subject panel, matched for age, sex and education. The same exclusion criteria were applied as in the patient group. Informed consent was obtained from all subjects.

TABLE 1 DETAILS OF THE INDIVIDUAL PATIENTS WITH PARKINSON'S DISEASE

| *Subject* | *Sex* | *Age (yrs)* | *Duration of illness (yrs)* | *Hoehn and Yahr rating* | *Levodopa (mg/day)* | *Other medication (mg/day)* | |
|---|---|---|---|---|---|---|---|
| 1 | M | 67 | 11 | III | 500 | — | |
| 2 | F | 67 | 16 | III | 500 | Orphenadrine | 250 |
| 3 | M | 71 | 11 | II | 500 | Orphenadrine | 250 |
| 4 | M | 61 | 14 | II | 400 | Benzhexol | 4 |
| 5 | M | 62 | 5 | II | 500 | — | |
| 6 | M | 55 | 20 | III | 500 | — | |
| 7 | M | 47 | 9 | II | 1000 | — | |
| 8 | M | 61 | 1 | I | 400 | Benzhexol | 4 |
| 9 | M | 43 | 10 | III | 500 | — | |
| 10 | M | 62 | 9 | II | 600 | — | |
| 11 | F | 60 | 10 | II | 400 | Amantadine | 200 |
| 12 | F | 64 | 28 | II | 500 | Benzhexol | 4 |
| 13 | F | 62 | 6 | II | 450 | — | |
| 14 | M | 56 | 11 | II | 800 | — | |
| 15 | F | 59 | 14 | III | 500 | — | |
| 16 | M | 67 | 11 | II | 1000 | — | |

*Assessment measures*

At the start of the session, each subject completed a set of visual-analogue scales measuring aspects of self-reported mood and alertness (Bond and Lader, 1974). In addition, each patient received a rating of illness stage (Hoehn and Yahr, 1967). At the end of the test session, each subject received a number of neuropsychological tests. These were two subtests of the Wechsler Adult Intelligence Scale (WAIS), Vocabulary and Block Design (Wechsler, 1955), the Wisconsin Card Sorting Test (WCST) (Nelson, 1976), the Purdue Pegboard Test (PPB) (Lezak, 1976), and the Paced Auditory Serial Addition Test (PASAT) (Gronwall and Wrightson, 1981). The last test can be considered a measure of focused attention. In the version used, subjects heard two recorded series of 30 single digit numbers. Their task was to add the most recent number to the number immediately preceding it, and to give the total. In the first series (PASAT-slow), a presentation rate of one digit every 4 s was used, while in the second (PASAT-fast), a rate of one digit every 2 s was used.

*Apparatus*

Stimulus presentation was via a colour visual display unit (VDU), controlled by a BBC (model B) microcomputer. The response apparatus comprised a box on which were mounted two buttons, one red and one green. The positions of these keys (left or right) were randomized across subjects. The subjects held the box in such a position that their thumbs could rest on the two buttons.

*The experimental tasks*

There were three experimental tasks: two Stroop tasks (a cued and a noncued version), and one Control task. Each subject received all three tasks. Standardized instructions for each task were presented via the VDU. For each task, the subject had the opportunity to watch examples and to practise. The experimenter was present throughout to ensure that the subject fully understood the tasks before proceeding to the main phase of each test. Each data collection phase lasted 10–15 min. Subjects received a break between each task. Half of the subjects within each group began with the Control task, and half with the Stroop tasks. Within the Stroop tasks, half received the cued version first, and half the noncued version.

*Stroop task: basic design.* The stimulus for each trial consisted of the word 'RED' or 'GREEN', presented in 2 cm high letters in the middle of the VDU screen. The stimulus 'RED' was presented in green letters, while the stimulus 'GREEN' was presented in red letters. During the standardized introduction to the test, the subject was taught that the two stimulus attributes were labelled 'Word' (the *meaning* of the stimulus word), and 'Ink' (the *colour* in which the stimulus was presented).

The main phase of the test comprised 101 trials. Immediately before commencing, the subject was informed whether the relevant stimulus attribute was 'Ink' or 'Word'. Half the subjects commenced with 'Ink' and half with 'Word'. If the relevant attribute was 'Ink', the subject had to ignore the meaning of the stimulus word, and respond by pressing the button corresponding to the colour of the 'ink' in which the word was presented. If the relevant attribute was 'Word', they had to ignore the colour of the 'ink' in which the word was presented, and press the button corresponding to the meaning of the stimulus word. The time from the appearance of the stimulus to the subject's response was taken as the reaction time (RT). Every 10 trials the command 'SWITCH' appeared on the VDU. This instructed the subject to ignore the previously *relevant* stimulus attribute, and respond instead to the previously *irrelevant* attribute The task was organized into 10 blocks of 10 trials, with half being 'Ink' blocks and half 'Word' blocks. The final trial (101) was a single trial of the next block in the alternating sequence. Within each block of 10 trials, half the correct responses were red and half were green. The order of red and green trials was randomized with this one constraint.

For each trial, the stimulus remained on the screen until the subject made a response, at which point the subject received immediately auditory feedback in the form of one of two distinct tones. One indicated a correct response, while the other signalled an error. The stimulus disappeared from the screen 1 s after the subject had responded.

*Stroop task: cued version.* Before each stimulus, the subject received the cue 'INK' or 'WORD', written in 2 cm high letters in the middle of the VDU screen. This cue served as a reminder of the currently relevant stimulus attribute. This cue was present for 1 s, after which it was replaced immediately by the trial stimulus. After the subject had responded and the stimulus had disappeared, there was an interval of 1.5 s before the next cue appeared.

*Stroop task. noncued version.* In this version, the cue preceding each trial stimulus was replaced by the word 'READY'. This served as a warning signal and simply allowed the subject to prepare to make a response.

*Control task.* In this task, two classes of stimuli were used. The first class consisted of the words 'RED' and 'GREEN', presented in white letters. The second class consisted of a rectangle (5 × 2 cm), presented centrally, coloured either red or green. The two types of stimuli were presented in 10 alternating blocks of 10 trials each with 1 further trial at the end Half of the subjects commenced with the words, and half with the rectangles. Subjects responded by pressing the button appropriate either to the colour of the rectangle or to the colour-name. As in the Stroop tasks, the subjects received auditory feedback on the accuracy of their response. After each block of 10 trials, the subject was warned of the change in stimulus class by the word 'SWITCH'. Before each stimulus the subject received the warning signal 'READY', as in the noncued Stroop task. The intertrial and intratrial intervals were the same as in the two Stroop tasks

### *Preliminary data handling*

The RT and error data for each subject was collapsed before further analysis. For the RT data, data from error trials were excluded. Each trial was designated a number from 1 to 10 according to its serial position in the block in which it occurred. Mean RTs of valid responses and mean errors were computed separately for 'Ink' and 'Word' trials for each of the 10 positions across the blocks. Thus each serial position RT or error score was the mean of a maximum of 5 individual responses. In computing the mean RT and errors scores trial 1 was discarded and replaced by trial 101. This was because the first trial of each block normally represented the 'alternation' trial, with the exception of the first trial. Trial 101 provided the tenth alternation trial. In order to reduce the number of variables entered into subsequent analyses, the scores were collapsed further. For both 'Ink' and 'Word' trials, mean RT and error scores were computed by taking the means for positions 2–4, 5–7 and 8–10. Finally, mean RT and error scores were computed for each block of 10 trials to assess performance across the course of each experiment. Where necessary, data were transformed to achieve more normal distributions before analysis.

### *Statistical methods*

Simple comparisons of group means were achieved using Student's t test for independent samples, or Mann-Whitney U tests. Analysis of the RT and error data in the Stroop and Control tasks was achieved using analysis of variance (ANOVA) for repeated measures using the MANOVA procedure of SPSS-X (SPSS Inc., 1983). Analyses of covariance were carried out where appropriate using the same procedure. Depending upon the analysis, either the multivariate statistic (Approximate F) or the univariate statistic (F) is reported. Where significant interactions were found, further post-hoc comparisons were conducted to elucidate the nature of the effect.

## RESULTS

Details of the two groups and their performance on the assessment measures are shown in Table 2. There was no significant difference between the mean ages of the two groups ($t=0.49$, $df=30$, $P=0.63$), their mean years of education ($t=0.90$, $df=30$, $P=0.34$), or the sex ratios ($\chi^2=0.13$, $df=1$, $P=0.72$). Of the assessment

TABLE 2 DETAILS OF THE TWO GROUPS AND THEIR PERFORMANCES ON THE ASSESSMENT MEASURES

| | *Parkinson group* *Mean (SD)* | *Control group* *Mean (SD)* | *P* |
|---|---|---|---|
| Age (yrs) | 60.3 (7.3) | 58.9 (8.5) | n.s. |
| Education (yrs) | 11.4 (2.5) | 12.3 (2.9) | n.s. |
| Duration of illness (yrs) | 11.6 (6.0) | — — | |
| Levodopa dosage (mg/day) | 566 (188) | — — | |
| Purdue Pegboard (total) | 30.8 (6.6) | 40.4 (4.3) | <0.001 |
| Affect-arousal score | 35.1 (22.7) | 22.4 (10.6) | n.s. |
| PASAT errors | | | |
| Fast presentation | 16.5 (6.8) | 10.9 (7.0) | <0.05 |
| Slow presentation | 12.9 (7.3) | 4.0 (5.0) | <0.001 |
| WAIS (scaled score) | | | |
| Vocabulary | 12.4 (2.9) | 14.2 (3.1) | n.s. |
| Block Design | 8.4 (2.7) | 11.9 (2.8) | <0.001 |
| WCST | | | |
| Categories | 3.3 (1.7) | 5.3 (1.3) | <0.01 |
| Nonperseverative errors | 12.9 (6.7) | 7.1 (6.1) | <0.05 |
| Perseverative errors | 5.4 (4.1) | 1.3 (1.9) | <0.001 |
| % Perseverative errors | 27.6 (12.5) | 11.3 (15.2) | <0.01 |

PASAT = Paced Serial Auditory Addition Test, WAIS = Wechsler Adult Intelligence Scale; WCST = Wisconsin Card Sorting Test, n.s = not significant ($P > 0.05$)

measures, the groups did not differ on WAIS Vocabulary (t = 1.71, df = 30, $P = 0.10$) while the difference in mean affect-arousal score just failed to reach significance (t = 2.02, df = 30, $P = 0.052$), with patients with Parkinson's disease reporting more adverse affect-arousal. For all of the remaining assessment measures, the Parkinson's disease group showed a significant impairment. These were WAIS Block Design (t = 3.58, df = 30, $P < 0.01$), Purdue Pegboard (t = 4.9, df = 30, $P < 0.001$), PASAT (slow) (t = 3.98, df = 30, $P < 0.001$), and PASAT (fast) (t = 2.27, df = 30, $P < 0.05$), and all aspects of performance on the WCST: categories (Mann-Whitney U = 46.0, z = 3.22, $P < 0.01$), nonperseverative errors (Mann-Whitney U = 64.0, z = 2.42, $P < 0.05$), perseverative errors (Mann-Whitney U = 38.5, z = 3.43, $P < 0.001$), and percentage perseverative errors (Mann-Whitney U = 43.5, z = 3.21, $P < 0.01$).

### *Reaction time*

Fig. 1 shows the mean RT for 'Ink' and 'Word' trials for the two groups, for each of the 4 partitions of within-block position of the 3 experimental tasks. Table 3 gives the overall group means collapsed across within-block positions, for 'Ink' and 'Word' trials for each of the three tasks.

Considering first the Control task, an ANOVA revealed significant main effects for Group (F(1,30) = 5.79, $P < 0.05$), and for Within-Block Position (Approx F(3,28) = 26.62, $P < 0.001$), but not for Stimulus Type ('Ink' or 'Word') (F(1,30) = 1.99, $P = 0.17$). None of the interaction effects was significant. Thus the patients with Parkinson's disease were slower than controls across both stimulus types and at each within-block position. Both groups showed equivalent changes

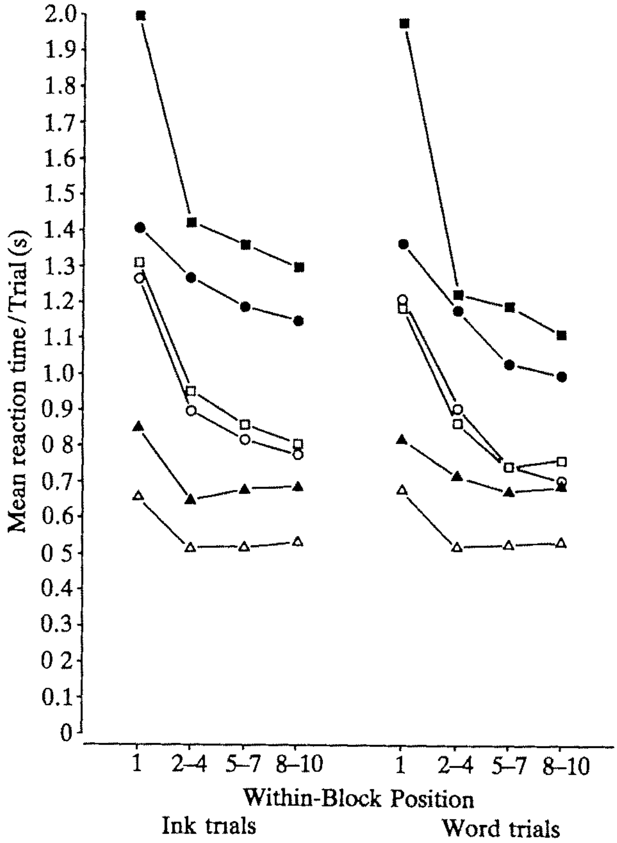

FIG. 1. Mean reaction times for trial positions within 'ink' and 'word' blocks, for the cued Stroop, noncued Stroop and control task in the Parkinson's disease and Control groups. Open figures = Control group; solid figures = Parkinson's disease group; squares = noncued Stroop task; circles = cued Stroop task; triangles = Control task.

TABLE 3. MEAN REACTION TIMES (IN SECONDS) OF THE TWO GROUPS ON 'INK' AND 'WORD' TRIALS FOR THE CONTROL TASK AND ON THE CUED AND NONCUED STROOP TASKS

| | *Parkinson group Mean (SD)* | *Control group Mean (SD)* |
|---|---|---|
| Control task | | |
| Ink (squares) | 0.69 (0.19) | 0.54 (0.19) |
| Word | 0.72 (0.21) | 0.56 (0.17) |
| Cued Stroop task | | |
| Ink | 1.22 (0.45) | 0.87 (0.29) |
| Word | 1.10 (0.30) | 0.83 (0.34) |
| Noncued Stroop task | | |
| Ink | 1.42 (0.47) | 0.92 (0.34) |
| Word | 1.27 (0.36) | 0.84 (0.28) |

in RT during the course of each block. Neither group showed any difference in the time taken to identify the colour of a shape and name a colour-word.

The ANOVA results for the Stroop tasks are shown in Table 4. Because of the large number of interaction effects, only 2-way and 3-way interactions involving Group were considered. Of the 3-way interactions, only the Group × Condition × Within-Block position effect approached significance ($P = 0.09$). This result will be considered further in the Discussion. Of the 2-way interactions, only the Group × Condition interaction was significant. Significant main-effects were shown for Group, Stimulus Type, Condition and Within-Block Position.

The absence of significant Group interactions involving either Within-Block Position or Stimulus Type, means that their two main effects can be interpreted unambiguously. First, across conditions and stimulus types, subjects in both groups became faster during the course of trials within each block. Analysis revealed a significant linear ($F(1,30) = 5.39$, $P < 0.05$), but not quadratic trend ($F(1,30) = 2.18$, $P = 0.15$). This may be considered as the establishment of a cognitive 'set' following each alternation. Secondly, across Conditions and Within-Block Positions, subjects of both groups were slower at identifying the colour of the 'Ink' with a competing word than they were at identifying the meaning of the 'Word' with a competing coloured ink. In the absence of any such difference in the Control task, this result confirms the findings of earlier studies on the Stroop phenomenon, that with competing stimulus attributes, word meaning produces greater interference than the colour of the ink in which the word is written. Nevertheless, it is clear from fig. 1 that both groups demonstrated substantial increases in RT in the Stroop conditions over the Control condition for both 'Ink' and 'Word' trials. Thus both Stroop and inverse-Stroop effects have been demonstrated in patients with Parkinson's disease as well as in normal controls.

The main effects for Condition and Group cannot be interpreted unambiguously in the light of the significant Group × Condition interaction. To explore the main effects, a series of post-hoc comparisons was performed. The results of analyses are shown in the bottom half of Table 4. First the RTs of the two groups were compared for the cued and noncued conditions in turn. Averaging across Stimulus Type and Within-Block Position, the Parkinson's disease group were significantly slower than the Control group in both the cued and the noncued conditions. Secondly, the two Stroop conditions were compared for each group in turn. In the Parkinson's disease group, averaging across Stimulus Type and Position, RTs were slower for the noncued than for the cued condition, whereas for the Control group, there was no difference between the RTs for the two conditions.

The main effects and interaction may be interpreted as follows. (1) The Parkinson's disease group were slower than the Control group under both cued and noncued conditions. (2) A differential effect of cueing on RT was found only in the Parkinson's disease group. The latter result may be a reflection of a fundamental cognitive deficit in Parkinson's disease. However, the patient group was impaired on the PASAT, a measure of general focused attention and also reported more

TABLE 4 RESULTS OF REPEATED MEASURES ANOVA FOR STROOP TASK REACTION TIME DATA

| *Effect* | *F* (*df*) | *P* |
|---|---|---|
| Main effects | | |
| Group (Parkinson's disease or Control) | 12.17 (1,30) | <0.01 * |
| Stimulus Type ('Ink' or 'Word') | 4.22 (1,30) | <0.05 * |
| Condition (cued or noncued Stroop) | 10.72 (1,30) | <0.01 * |
| Within-Block Position (1–10) | 23.52 (3,28) | <0.001* |
| Two-way interactions | | |
| Group × Stimulus Type | 0.41 (1,30) | 0.52 |
| Group × Condition | 6.82 (1,30) | <0.05 * |
| Group × Within-Block Position | 0.19 (3,28) | 0.89 |
| Three-way interactions | | |
| Group × Stimulus Type × Condition | 0.02 (1,30) | 0.89 |
| Group × Stimulus Type × Within-Block Position | 0.33 (3,28) | 0.80 |
| Group × Condition × Within-Block Position | 2.40 (3,28) | 0.09 |
| Post-hoc partition of interaction effects | | |
| Cued Stroop. Group comparison | 6.01 (1,30) | <0.05* |
| Noncued Stroop. Group comparison | 16.15 (1,30) | <0.001* |
| Parkinson group cued/noncued comparison | 17.33 (1,30) | <0.001* |
| Control group cued/noncued comparison | 0.22 (1,30) | 0.64 |

* Significant result ($P<0.05$).

adverse affect-arousal than the controls. As either of these variables might conceivably have influenced test performance, the above analyses were repeated with total PASAT errors and affect-arousal score as covariates. The analyses revealed that total PASAT error score was not a significant covariate for either Group (F(1,29) = 1.50, $P=0.23$) or for the Group × Condition interaction (F(1,29) = 1.44, $P=0.24$). Similarly, affect-arousal was not a significant covariate for either of the two effects (F(1,29) < 0.01, $P=0.99$, and F(1,29) = 0.04, $P=0.84$, respectively). Thus neither of these variables could account for the group differences or interactions. To determine whether these effects were due to the same cognitive functions being tapped by the WCST, the above analyses were repeated using percentage perseverative errors as a covariate. This measure was chosen above the other WCST indices as it was felt to be most relevant to performance on the Stroop tasks. This measure, however, did not prove to be significant covariate for either the main effect of Group (F(1,29) = 0.32, $P=0.57$) or for the Group × Condition interaction (F(1,29) = 2.57, $P=0.12$). This suggests that factor being tapped by the WCST is not making a significant contribution to the impaired performance observed on the Stroop tests.

Any group differences in RT on the two Stroop tasks must be interpreted with respect to differences in RT found with the non-Stroop Control task. The slowness of the Parkinson's disease group in the Control task may be attributed to slowness in any or all of the stages of planning, initiating or executing the motor response, and/or in the speed of perceptual analysis of the stimulus. Whatever the cause, this basic psychomotor slowness must be taken into account when interpreting the RT

TABLE 5. RESULTS OF REPEATED MEASURES ANOVA FOR STROOP TASK REACTION TIME DATA AFTER SUBTRACTING REACTION TIME FOR CONTROL CONDITION

| *Effect* | *F (df)* | *P* |
|---|---|---|
| Main effects | | |
| Group (Parkinson's disease or Control) | 8.95 (1,30) | <0.01 * |
| Stimulus Type ('Ink' or 'Word') | 5.40 (1,30) | <0.05 * |
| Condition (cued or noncued Stroop) | 10.73 (1,30) | <0.01 * |
| Within-Block Position (1–10) | 17.73 (3,28) | <0.001* |
| Two-way interactions | | |
| Group × Stimulus Type | 0.21 (1,30) | 0.65 |
| Group × Condition | 6.83 (1,30) | <0.05 * |
| Group × Within-Block Position | 0.32 (3,28) | 0.81 |
| Three-way interactions | | |
| Group × Stimulus type × Condition | 0.02 (1,30) | 0.89 |
| Group × Stimulus Type × Within-Block Position | 0.71 (3,28) | 0.56 |
| Group × Condition × Within-Block Position | 2.40 (3,28) | 0.09 |
| Post-hoc partition of interaction effects | | |
| Cued Stroop. Group comparison | 2.41 (1,30) | 0.13 |
| Noncued Stroop. Group comparison | 12.71 (1,30) | <0.01 * |

* Significant result ($P < 0.05$)

differences observed between the two groups in the Stroop tasks. To explore this, RT for the Control task was subtracted from that for the two Stroop tasks for each subject. The results of the subsequent ANOVA are shown in Table 5. None of the 3-way interactions was significant. Of the 2-way interactions, as before only the Group × Condition interaction was significant. Finally, significant main effects were shown for Group, Stimulus Type, Condition and Within-Block Position. Thus even after 'controlling' for basic psychomotor slowness, the Parkinson's disease group were still slower overall than the controls, indicating an increased time in carrying out the cognitive activities required in the Stroop tasks. As before, the Group × Condition interaction was significant, so post hoc Group comparisons were performed separately for each of the two Stroop tasks to aid interpretation. The outcomes are shown in the bottom half of Table 5. The ANOVAs revealed significant Group differences for the noncued Stroop condition, but not for the cued Stroop condition. Thus, after taking into account basic psychomotor slowing, the RT of patients with Parkinson's disease was impaired only in the noncued version of the Stroop task.

Having analysed the within-block position effects, the between-block effects were next assessed. Before analysis the data were collapsed by taking the average RTs of successive pairs of blocks (i.e., 1 and 2, 3 and 4, etc.). Each averaged block-pair thus corresponded to the mean RT for one block of 'Ink' trials and one block of 'Word' trials. Fig. 2 shows the mean RT for the two groups for each of the 5 block-pairs in the cued and noncued Stroop tasks. It revealed no appreciable trends in either group for the control task. Analysis was therefore restricted to the Stroop tasks. Repeated-measures ANOVA showed significant main effects for Group

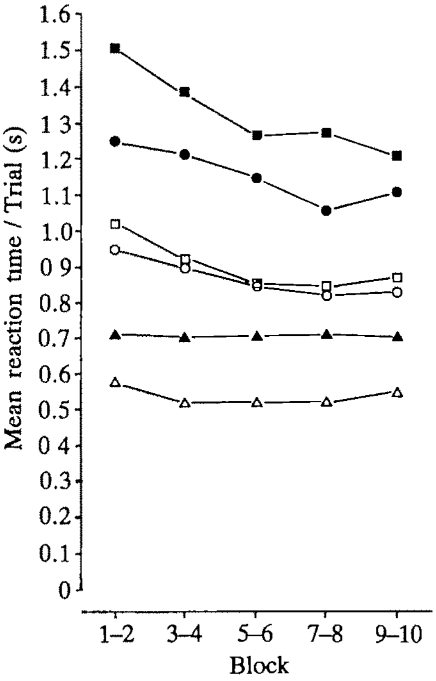

FIG 2. Mean reaction times for successive block pairs, for the cued Stroop, noncued Stroop and control task in the Parkinson's disease and Control groups. Open symbols = Control group; solid symbols = Parkinson's disease group, squares = noncued Stroop task; circles = cued Stroop task; triangles = Control task

(F(1,30) = 9.36, $P<0.01$) and for Stroop condition (F(1,30 = 8.13, $P<0.01$). A significant Block effect was also found (Approx F(4,27) = 10.18, $P<0.001$). However, neither the Group × Block (Approx F(4,27) = 0.84, $P=0.51$) nor Group × Condition × Block effects (Approx F(4,27) = 0.74, $P=0.58$) were significant. Thus both groups, for both Stroop conditions, showed a shortening in RT across the course of each task. No difference was found between the two groups in the nature of this change.

### *Errors*

Because of the relatively low error rates in the Stroop tasks, particularly for the Control group, it was not viable to partition the within-block error data in the same way as was used for the RT data. Instead they were collapsed into a number of larger partitions and the different effects tested separately. Before the analyses, the various sets of collapsed error scores were subjected to square-root transformation. Errors in the non-Stroop Control task were extremely rare in either group and were not considered in the analysis.

First, four error scores were calculated for each subject. These were total errors for the 'Ink' trials and for 'Word' trials in each of the two Stroop conditions, cued and noncued. The transformed data are shown in fig. 3. Repeated measures ANOVA revealed significant main effects for Group (F(1,30) = 23.52, $P<0.001$), for Condition (cue/noncue) (F(1,30) = 5.01, $P<0.05$) and for Material (ink/word) (F(1,30) = 13,80, $P<0.01$). Significant two-way interactions were found for Group

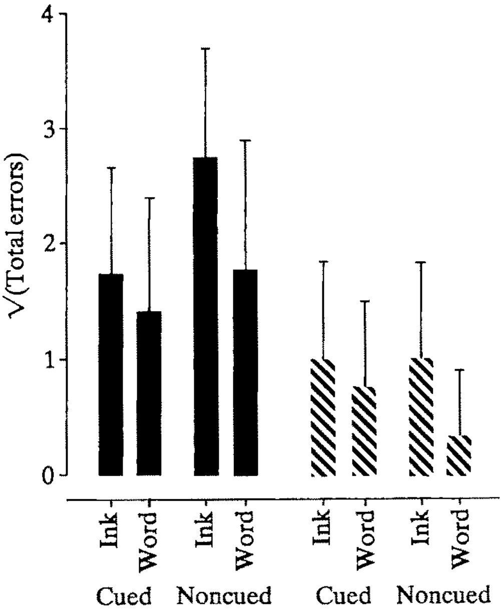

FIG 3 Total errors (√) (+1 SD) for 'ink' and 'word' trials, for the cued and noncued Stroop tasks, in the Parkinson's disease and Control groups. Cross-hatched bars = Control group; solid bars = Parkinson's disease group

× Condition (F(1,30) = 14.05, $P < 0.01$), but not for Group × Material (F(1,30) = 0.12, $P = 0.73$). The 3-way interaction Group × Condition × Material was not significant (F(1,30) = 0.08, $P = 0.78$). The results from the error data thus parallel those from the RT data. As error rates in the control group were low, the above analysis might be influenced by floor-effects. To check this, the analysis was repeated using percentage error rates. The results were substantially the same as achieved when using absolute error rates.

Before further analyses, the main effect of Group and the Group × Condition interaction were reassessed with PASAT and effect-arousal as covariates. PASAT was not found to be a significant covariate for either the main effect (F(1,29) = 0.01, $P = 0.93$) or for the interaction (F(1,29) = 0.001, $P = 0.97$), while affect-arousal was a significant covariate in the case of the main effect of Group (F(1,29) = 7.05, $P < 0.05$) but not for the Group × Condition interaction (F(1,29) < 0.10, $P = 0.77$). However, even when adjusted for affect-arousal, the Group difference was still highly significant (F(1,29) = 16.54, $P < 0.001$). Once again, WCST percentage perseverative errors were also used as covariates. As with RT, this measure was not a significant covariate either for the main effect (F(1,29) = 0.74, $P = 0.52$) or for the interaction (F(1,29) = 1.59, $P = 0.22$).

In order to interpret the data in the light of the significant Group × Condition interaction, the groups were compared for each Stroop condition in turn. Results revealed significant differences between the groups for both the cued (F(1,30) = 6.98, $P < 0.05$) and for the noncued condition (F(1,30) = 38.30, $P < 0.001$). Next the effect of Stroop condition was assessed for each group in turn. The Parkinson's disease group made significantly more errors in the noncued than in the cued condition (F(1,30) = 17.92, $P < 0.001$), while the performance of the controls did not differ

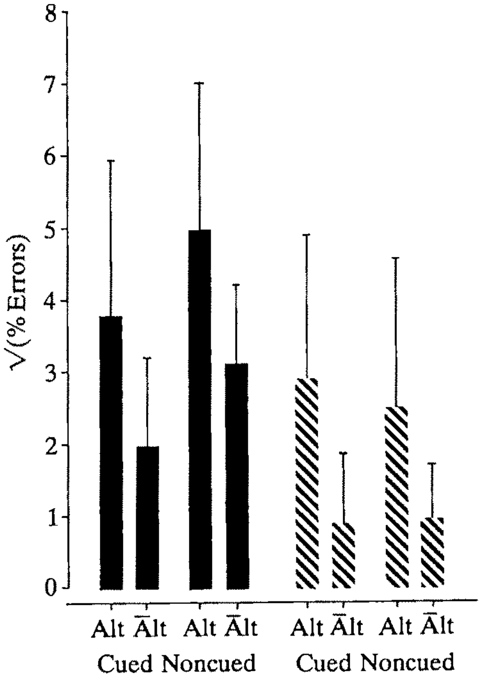

FIG 4 Percentage Alternation and Non-Alternation errors (√) (+1 SD), for the cued and noncued Stroop tasks, in the Parkinson's disease and Control groups. Cross-hatched bars = Control group; solid bars = Parkinson's disease group.

for the two Stroop tasks (F(1,30) = 1.14, $P = 0.29$). Thus while the patients made more errors than the controls overall, they made a disproportionate number of errors in the noncued condition. Table 5 also shows the Group × Within-Block Position interactions for each Stroop task individually. In neither case was the interaction significant.

Errors on the Stroop tasks can be considered as falling into two main classes. The first comprises those errors which occur on trial 1 of the block. These *alternation errors* imply that the subject was unable to use the instructions given, to switch attention from one stimulus attribute to the other. Errors committed on trials in positions 2–10 of each block can be designated *nonalternation errors*. The data for these two classes of errors are shown in fig. 4. Because each Stroop Condition contained 90 nonalternation trials, and only 10 alternation trials, the error data is expressed as a percentage of the maximum number of possible errors that could be made of each, to permit a meaningful comparison between the error-types.

Repeated measures ANOVA revealed significant main effects for Group (F(1,30) = 14.96, $P < 0.001$), for Condition (cue/noncue) (F(1,30) = 4.49, $P < 0.05$) and for Error-Type (alternation/nonalternation) (F(1,30) = 45.24, $P < 0.001$). Neither the Group × Condition × Error-Type interaction (F(1,30) = 0.54, $P = 0.47$) or the Group × Error-Type interaction (F(1,30) = 0.001, $P = 0.98$) were significant. As before, the Group × Condition was significant (F(1,30) = 8.46, $P < 0.01$). Thus the Parkinson's disease group made more errors of both types than did the controls, but the difference between percentage alternation and nonalternation errors was the same for both groups. In the absence of a significant Group × Error-Type interaction, and given that the main effect for Group has already been shown to be robust, the ANOVA was not repeated with covariates.

Finally, a comparison was made between the mean number of errors made by the two groups in the two halves of each experimental condition. Significant main effects were found for Group (F(1,30) = 23.96, $P < 0.001$) and for Condition (F(1,30) = 10.37, $P < 0.01$) but not for First/Second Half (F(1,30) = 2.22, $P = 0.15$). Neither the Group × Half (F(1,30) = 0.56, $P = 0.46$) or the Group × Condition × Half interactions (F(1,30) = 2.41, $P = 0.13$) were significant. Thus neither group showed any change in error rate, in either Stroop condition, between the first and second half of each task.

### *Summary of main results*

1. The patients with Parkinson's disease were impaired on the WAIS block design test and the WCST. In addition, they reported a more adverse affect-arousal state than the controls, and showed impaired attention as measured by the PASAT. In contrast, the patients were unimpaired on the WAIS Vocabulary Test.
2. The patients with Parkinson's disease were slower than the controls on all RT tasks. In contrast to the control group, the patients were slower in the noncued Stroop condition than in the cued condition. After allowing for basic psychomotor slowing, the patients were significantly impaired only on the noncued task in terms of the RT data. Both groups showed equivalent increases in RT with alternation between blocks, and similar decreases with repetition of the same stimulus type. Both groups showed similar Stroop interference effects. Neither the affect-arousal state or attention as assessed by the PASAT appeared to contribute to the pattern of group differences and interactions in the RT data.
3. The patients with Parkinson's disease made more errors than the controls in both Stroop tasks, although the difference was greatest for the noncued condition. There was no tendency for the patients to make a disproportionate number of errors on any one type of trial, either alternation or nonalternation. Neither group showed any consistent change in error rate between the two halves of each Stroop condition. Finally, neither the affect-arousal state nor attention, as measured by the PASAT, contributed to the pattern of group differences or interactions in the error data.

## DISCUSSION

The primary aim of the present study was to test the hypothesis that patients with Parkinson's disease are impaired on tasks where they have to rely upon internal control for regulating attentional processes, but are relatively unimpaired when given external cues. The study also permitted the testing of two additional (although not entirely separate) hypotheses. The first was that patients with Parkinson's disease have a deficit in the switching and/or maintenance of cognitive set. The second was that they may be abnormally sensitive to Stroop-type interference, in the same way as patients with damage to the prefrontal cortex.

### *Stroop-type interference in Parkinson's disease*

The second hypothesis will be considered first. In the Introduction, the distinction was drawn between the Stroop effect and the inverse-Stroop effect. Which effect is shown depends upon whether the subject is being asked to identify the colour of the ink in which the word is written, or the meaning of the word. The present experiment, using an alternating paradigm, was able to demonstrate both Stroop and inverse-Stroop effects in patients with Parkinson's disease and normal controls, with the former effect being larger. As the difference between the two effects was the same in both groups, they will not be considered separately, but will be called simply 'Stroop-type interference'.

Susceptibility to Stroop-type interference has been shown to be increased following brain damage (Golden, 1976; Dodrill, 1978), particularly to the frontal lobes (Perret, 1974; Stuss *et al.*, 1981). The Stroop task has also been given previously to patients with Parkinson's disease (Portin and Rinne, 1980; Hietanen and Teräväinen, 1986). Unfortunately, in neither study were the data analysed to separate Stroop interference from basic psychomotor slowing. Thus only the present study provides evidence on the Stroop effect in Parkinson's disease. If the magnitude of the interference effects is indicated by the differences between identifying stimuli in the competing attribute (Stroop) and control conditions, then the patients showed an abnormal amount of interference relative to the controls only on the noncued task, at least with regard to RT. In terms of errors, patients made more errors in both conditions, but the greatest impairment was shown once more in the noncued condition. This suggests that increased susceptibility to Stroop-type interference is not an inevitable consequence of Parkinson's disease. Rather it is found primarily in those situations where the patient has to rely on internal cues for the control of attention. In other words, the deficit on Stroop tasks may be simply a reflection of the more fundamental deficit which was hypothesized in the Introduction. Whether the same is true of patients with frontal lobe damage is unknown. However, in general, patients with such damage are maximally impaired on those tasks where they have to rely on self-generated strategies for planning and organizing behaviour, while their performance may be improved by externally provided plans and cues (Stuss and Benson, 1984). In other words, they show the same pattern of deficits which it is proposed characterizes the performance of patients with Parkinson's disease.

### *Alternation and maintenance of cognitive set in Parkinson's disease*

Did the patient's performance on the Stroop tasks indicate any deficits in the processes of alternating and/or maintaining cognitive set? The main investigation of cognitive set in the present study was concerned with changes in within-block performance. Cognitive set can be defined as the facilitation in performance found with the repetition of a rule by which a set of stimuli is associated with a set of responses. In the present task, the stimulus-response mapping rule changed every 10 trials. Any decrease in RT and/or error rate, seen within each block of trials, could be taken as evidence of the establishment of the cognitive set. Averaging across the two Stroop conditions, the analyses revealed no significant Group × Within-Block Position interaction effect, suggesting that the two groups did not differ overall in the average shapes of the curves indicating the establishment of the cognitive set. However, while there was no significant Group × Within-Block Position interaction effect, the results indicated a 3-way Group × Within-Block Position × Stroop Condition effect which approached significance. From fig. 1 it is clear that the shapes of the curves for the control group in the two Stroop conditions are virtually identical. However, the cued and noncued curves for the patient group suggest that the effect of cueing/noncueing was maximal for trials in position 1 averaged across blocks. Thus, in as much as the first trial in each block represents the trial after alternation between one stimulus attribute to the other, this result offers some support for the theory that the patients had some difficulty in switching set in the noncued condition. This implies that the patients cannot be considered to have a generalized switching deficit, even in tasks where there are competing stimulus attributes. The theory of Cools *et al.* (1984) therefore seems untenable. While showing some difficulty in shifting in the noncued condition, it is clear that once the shift was made, the patients were still able to make considerable savings in performance with the course of each block. It is possible that if the block sizes were larger, performance might have deteriorated, but there was no evidence from the present study that the patients had any difficulty in maintaining set.

### *Internal and external cues and the control of attention in Parkinson's disease*

This brings us to the central hypothesis of this study, namely the role of internal versus external cues in attentional control processes. The test of this hypothesis lay in any difference between the cued and noncued Stroop conditions. The results revealed that the control group showed no difference in either mean RT or error rate for the cued and noncued tasks. This implies that either (1) the controls were ignoring the external cues in the cued condition and relying instead, in both tasks, on internal cues, or (2), they were attending to the external cues, but that the latter were no more or less effective than their own internal cues. In contrast, the patients with Parkinson's disease showed significant differences in their performance under the two conditions, with an increase in mean RT and error rate in the noncued condition.

The crucial component of the Stroop tasks which was of interest here, was the presence of a stimulus with two competing attributes which required the subject to focus attention on one and ignore the other. To assess the impact of this added attentional demand, the Control task was designed to assess the time taken for subjects to evaluate and respond to each attribute independently. Comparing the groups under the two Stroop conditions, after controlling for basic psychomotor speed as revealed by the Control task, indicated that the RTs of the Parkinson's disease group in the cued condition did not differ significantly from those of the controls. It was only in the uncued condition that the RTs of the Parkinson's disease group were abnormal. While they made significantly more errors under both Stroop conditions, the difference in errors between the groups in the cued condition was relatively small compared with that for the noncued condition.

The results therefore support the hypothesis that the locus of attentional control is an important fact in determining the presence and/or magnitude of cognitive deficit in Parkinson's disease, at least for the tests employed in the present experiment. The question which remains to be answered is whether the fundamental deficit underlying the result of this study is related directly or only incidentally to the internal source of the cue being used to control attention.

### *Models of working memory and attentional control*

While we have a working hypothesis defining the operational nature of the deficits, we do not yet have a model to explain the process involved. The value of any model should be judged in two ways: first, the degree to which it fits with and increases our understanding of already existing data; secondly, its power to generate further testable hypotheses. Potentially the most useful models for our present purposes are those of Working Memory (Baddeley, 1986) and the model of attention developed by Norman and Shallice (1980). After briefly explaining the nature of these models, we shall attempt to fit them to the results from the present study.

When we perform any cognitive task, we need to access and process information from the current environment together with the information contained in long-term store. Obviously an interface is required for those different types of information. This interface has been labelled 'working memory'. It is seen as being divided into a 'central executive' and a number of 'slave systems'. These latter systems include an 'articulatory loop' which permits the recycling of verbal information while it is being processed, and a 'visuospatial sketchpad' which permits the temporary storage and manipulation of visuospatial information. Within the framework of Working Memory, investigation has focused mainly on these slave systems. The central executive is seen as acting as a supervisor or scheduler, selecting strategies and integrating information from several different sources. Its precise nature and characteristics, however, have not been elaborated to the same degree of those of the slave systems (Baddeley, 1986). The role of the central executive can be seen as overlapping with the function of attentional control, dividing attention between different sources of internal and external information. This led Baddeley (1986) to adopt the attentional model of Norman and Shallice (1980) and apply it to the central executive. Norman and Shallice proposed a model of attentional control within the framework of action. Many actions, such as walking, are automatic. Sets of motor programs controlling individual muscles form higher order motor plans or schemata which can be executed without conscious effort. Several different schemata or plans may run in parallel, allowing us to perform different tasks simultaneously. There will be times, however, when the different schemata will conflict. The model proposes an automatic processor or 'contention scheduler' which gives precedence to one of the conflicting schemata at any one moment on the basis of preset priorities and environmental contingencies. It is clear, however, that we can override automatic action and consciously focus our attention elsewhere. Norman and Shallice (1980) proposed a 'supervisory attentional system' (SAS) to serve this function. The SAS is assumed to have limited capacity and is therefore called upon only under certain situations. These include (1) planning and decision making, (2) novel or poorly learned tasks and where preprogrammed schemata are not available, and (3) situations where some strong habitual response or temptation is involved. The functional distinction between the contention scheduler and SAS can be seen as equivalent in some ways to the distinction made by Shiffrin and Schneider (1977) between automatic and controlled processes.

Baddeley (1986) proposed that the SAS may be equated with the central executive. In particular, the concept of a central scheduler with limited processing resources is common in both models. It is in understanding cognitive deficits in various patient groups that this approach has proven most fruitful. Shallice (1982) suggested that the cognitive deficits shown by patients with frontal lobe lesions may be understood in terms of deficit in the SAS. Deficits are most likely to be found when the patient is required to plan or handle novel situations, and make changes when task demands alter. Recent work has extended the investigation to patients with Alzheimer's disease (Baddeley *et al.*, 1986).

### *Application of the models to the deficits found in Parkinson's disease*

The Stroop task places a large attentional demand on the subject. The subject must select one of two stimulus attributes, while attempting to inhibit the other. In the version used in the present experiment, the demands are greater still as the relevant attribute is not constant. Such a task might therefore be expected to rely heavily upon the SAS. If the SAS were to break down or become overloaded, then the subject might revert to responding to the previously rather than currently relevant attribute. In order for the SAS to work efficiently it needs information on the current status of the task. The results from the present experiment suggest that when that information was provided from an external source, the SAS of patients with Parkinson's disease was able to function relatively normally. When it had to rely on internally generated information, however, more errors were committed and processing time increased. What might be going wrong to explain these deficits? Two main possibilities exist. The first relates to the nature of the information which the SAS is using; the second relates to the characteristics of the SAS itself.

The present study was designed to assess the hypothesis that the nature of the cues controlling attention were an important determinant of cognitive dysfunction in Parkinson's disease. Thus within the framework of Working Memory being proposed here, the deficit may not lie with the SAS itself, but with the internal information which it has to utilize. It is possible that this information is stored in a degraded or disorganized way. The result of this might be slower and less accurate retrieval of that information by the SAS from short-term memory. Evidence for a deficit in short-term memory in Parkinson's disease is, however, equivocal. In the majority of studies immediate digit span is unimpaired (e.g., Asso, 1969; Horn, 1974; Riklan *et al.*, 1976; Lees and Smith, 1983; Hietanen and Teräväinen, 1986). An experiment by Tweedy *et al.* (1982), however, assessed the recall of work triads using the Brown-Peterson short-term memory paradigm. While the patients' immediate recall was normal, they showed impaired performance after intervals of only 3 to 18 s when the delay was filled with a task to prevent rehearsal. In the present experiment, the subjects were free to employ rehearsal as a strategy to maintain the cue given at the beginning of each block, in a salient and useable form. It is possible that the patients with Parkinson's disease fail to employ such a strategy, although there is no direct evidence to support this hypothesis. The role of a short-term memory deficit underlying the present results is therefore unclear.

Other possible explanations lie with the SAS itself. While the information may be available, the SAS may have difficulty in accessing and/or using it to control attentional resources. A utilization deficit is unattractive, however, as it requires that we postulate different mechanisms in the SAS for dealing with information from different sources, internal or external. A deficit in accessing the internal information is more appealing. Presumably different pathways are involved in accessing stored information, and that coming directly from cortical association areas. Experiments might therefore be devised to measure the speed and efficiency of access to the internal information as distinct from its utilization.

At this point a note of caution is necessary. The discussion so far has postulated two separate pathways through which the SAS derives its information, only one of which is impaired in Parkinson's disease. Norman and Bobrow (1975) suggested that, in general, a dissociation between performance on two tasks does not necessarily imply differences in the functioning of two systems or subsystems. It is possible that the results derive merely from a quantitative difference in the resource requirements of the two tasks. As noted above, the SAS is seen as having limited resources. These resources would be allocated according to the task demands. At some point, however, if task demands continued to increase, they would outstrip the resources and performance would decline. In the present experiment, the control subjects performed equally well on the cued and noncued Stroop tasks. This does not necessarily imply that they demanded equivalent attentional resources, but only that the demands made by each task were within the available capacity of the SAS. The hypothesis that the cued and noncued Stroop tasks require different levels of the SAS's attentional resources can easily be tested by a standard Working Memory paradigm. The subject could be given a second attention-demanding task to perform at the same time as the primary Stroop tasks. If this secondary task were sufficient to overtax the SAS then control subjects should show a difference in performance on the two Stroop tasks, if indeed they were placing differential demands on the attentional resources of the SAS. In Parkinson's disease, the natural resources of the SAS may be depleted. With a task making moderate demands within the limited resources, performance would be relatively normal. On a more difficult task such as the noncued Stroop, as demand overstretched with depleted resources, performance would decline. Furthermore, in the Working Memory paradigm the level of secondary task load needed to overtax the SAS should be less than that needed for the normal control subjects. The resource model of the SAS therefore fits the observed data well and can generate several testable predictions.

So far the discussion has focused on the role of the SAS. What role might the contention scheduler play in the Stroop task? One possibility is that it may make use of redundancies resulting from repetition of the same class of cognitive events to increase processing efficiency before the stage where the SAS functions, that is, it may be responsible for the phenomenon of cognitive set, at least as defined in the present study. As noted above, the SAS is seen as being involved in novel situations, or where habitual tendencies have to be overcome. With repeated exposure to the same task, the novelty decreases and new habitual tendencies become established. A degree of control may therefore pass over from the SAS to the contention scheduler with the corresponding decrease in RT. This serves as a plausible model to explain the repetition effects of the type observed in the present experiment which we have labelled 'cognitive set'. Thus the demands on the SAS should be maximal in position 1 of each block, and should decrease with each repetition. As noted above, it was in position 1 of each block that the difference between the cued and noncued Stroop conditions were greatest in the Parkinson's disease group. This supports the notion of a deficit in the SAS resources. It implies further, however, that the more automatic functioning of the contention scheduler is relatively intact. The slopes of the lines of fig. 1 can be taken to represent the gradual transfer of control from the SAS to the contention scheduler. The analysis reported in Table 5 suggests that in neither the cued nor the noncued condition was the rate of transfer different in the two groups.

In the Introduction the hypothesis that cognitive deficits in Parkinson's disease were related specifically to reliance upon internally generated cues was chosen in preference to the theory of Weingartner *et al.* (1984) based on the concept of 'effort' and a continuum of automatic to controlled cognitive processes. How do these models stand in the light of the present results and subsequent discussion? While the internal-external distinction was shown to be a valid parameter for predicting cognitive deficit, the application of the Working Memory model and, in particular, the role of the SAS, seems to suggest that the importance of the source of the cues may lie in the differential attentional demands which they place on the SAS's limited resources. If 'attentional demanding tasks' are relabelled 'effort demanding tasks' then we might seem to have returned to the model of Weingartner *et al.* (1984) who proposed a single dimension from automatic to controlled. The new model sees this apparent continuum as the coordinated action of two separate levels of processing, the contention scheduler and the SAS. Secondly, the Weingartner model predicts a linear relationship between effort demands and performance decrement. Our model suggests that there is a threshold which must first be crossed before such a relationship becomes apparent. Provided attentional resources are not overstretched, performance will be maintained despite increases in task demands. This concept of a threshold would be of little value without the means to test it empirically for individual tests. The paradigms developed to assess Working Memory provided us with the tools to do just that (Baddeley, 1986). Using those methods it should be possible to determine the characteristics of Working Memory in Parkinson's disease and its relationship to other aspects of cognitive function.

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# AN INVESTIGATION INTO PERCEPTUAL COMPLETION IN BLIND AREAS OF THE VISUAL FIELD

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## SUMMARY

The perceptual completion phenomenon refers to seeing a figure as complete when part of it falls in a blind area of the visual field. This phenomenon and the conditions for its occurrence were examined in three different situations: over the retinal blind spot, across the midline of the visual field in commissurotomized patients, and in the blind visual field in hemianopic patients. Responses of complete perception were obtained in each of the three conditions, but they were not all the result of a genuine perceptual completion process. Reports of vision over the retinal blind spot qualified as genuine perceptual completion. In the other two situations, reports suggestive of completion could be entirely eliminated in all but one hemianopic patient by manipulating parameters inherently involved in the evaluation of perceptual completion. The nature of perception, the characteristics and properties of the experimental task and stimuli, the mode of response, the patient's mental status, and eccentric eye fixation, all contributed towards reports of complete perception for reasons other than a process of completing the missing information. Evidence of completion was found in one patient who could see more distinctly in his affected field with bilateral stimulation than with stimulation of the affected field alone. The results suggest that perceptual completion in the hemianopic field is not a common phenomenon and that reports of complete perception are determined by many factors, not all related to seeing more than is objectively available. The results also indicate that the hemianopic defect does not function as an extended blind spot. Possible mechanisms underlying perceptual completion over the blind spot and the hemianopic field are suggested.

## INTRODUCTION

Perceptual completion is the process of filling in the missing information when part of a figure falls in a blind area of vision. It implies the capacity to see more than is objectively available and suggests that the emerging percept is not a one-to-one mapping of the pattern of stimulation within the retinotopically organized visual cortex. Support for the existence of perceptual completion comes from three independent sources. One is the fact that, in monocular viewing, the presence of a blind area in the visual field corresponding to the retinal blind spot is often not noticed, suggesting completion of the missing information in accordance with the

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surrounding pattern of activation (Le Grand, 1967). A second source of evidence comes from studies on commissurotomized patients. When presented, for example, with two juxtaposed half-faces straddling the centre of the visual field such that each half-face projects only to one hemisphere, these patients report seeing one full face, and sometimes even two superimposed full faces (Levy *et al.*, 1972), even though each disconnected hemisphere is actually stimulated with only half a face. The third, and best documented evidence for perceptual completion is the reported capacity of hemianopic patients to fill in images, part of which falls in the blind area of their visual field (Poppelreuter, 1917; Warrington, 1962; Gassel and Williams, 1963).

This phenomenon is regarded as reflecting a basic property of the visual system whereby what is seen may not be entirely determined by sensory cortical activation (e.g., Crick, 1979; Shepard, 1984). Yet, while it is established that perception involves an active interpretation of sensory signals that are complemented and enriched by past experience and expectations and thus give rise to the emergence of meaningful external objects or scenes (Blakemore, 1975; Gregory, 1977; Rock, 1983), it is less clear how a pattern can be seen as complete in the absence of parts of its physiological substrates. The purpose of this paper is to consider in turn each of the three sources of evidence of perceptual completion in an attempt to examine the conditions that determine its occurrence and, when possible, to specify some of its underlying mechanisms. It must be noted that 'perceptual completion' does not refer to the capacity to tell the identity of an object despite missing parts in the figure but to the capacity actually to see the part of the figure falling in the blind area of vision, as a function of the adjacent pattern of stimulation. In the first part, a simple demonstration of perception across the blind spot is described, providing the reader with a self-experiment on the phenomenon. The second and third parts present the results of experiments conducted on commissurotomized and hemianopic patients aimed at determining the various factors that contribute to the emergence of perceptual completion.

## PERCEPTION ACROSS THE BLIND SPOT

The blind spot of each eye results from axons of ganglion cells and blood vessels passing through the retina at the optic disc and, in the process, depriving this retinal area of receptors. Its centre is located at a distance corresponding to 15.5° from the fovea, in the nasal half of the retina, and 1.5° below the horizontal meridian. It is 5.5° wide and 7.5° high (Harrington, 1981). Because the left and the right blind spots are symmetrically located with respect to the sagittal plane, the information falling on the blind spot of one eye stimulates a sensitive area of the other eye. Only in monocular viewing is there a blind area in one visual field, temporal to fixation.

The presence of a blind spot is easy to demonstrate. When looking with the right eye at the vertical of the left dot in fig. 1A from a distance of about 35 cm, the larger

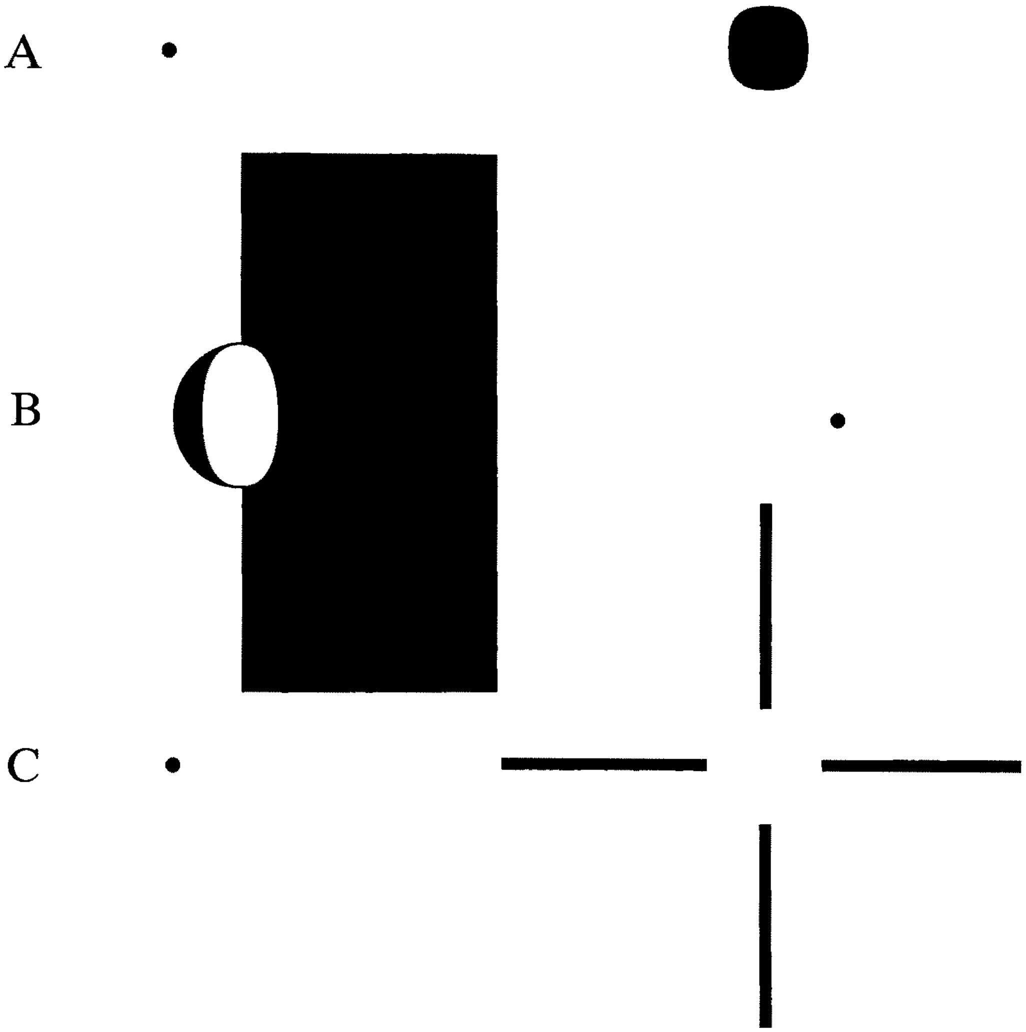

FIG. 1. Three patterns for demonstration of perceptual completion over the blind spot (*see* text for explanation)

dot on the right falls out of view as it projects on the blind spot. However, the blind area is not seen as a hole or as a dark spot, but looks homogeneous with its immediate surroundings which seem to 'invade' the blind area. In fig. 1B, the white half-oval located on the left of the large black stripe fails to be perceived when looking with the left eye at the small right dot from an appropriate distance, and the stripe appears to run vertically through the normally blind area. This completion is determined by the immediate neighbourhood and does not extend across the whole blind area as the left part of the oval is surrounded by a white surface. In fig. 1C, when looking at the left dot with the right eye, the gap in the centre of the converging lines disappears and the observer seems to perceive two continuous orthogonal lines. Yet the virtual junction point which should form a cross appears somewhat indistinct, even though the vertical and the horizontal lines can be perceived as continuous. It is also noteworthy that completion requires the presence of a line on each side of the blind area; if one of the horizontal lines is covered, the perceived line stops at the border of the blind spot.

These simple demonstrations suggest that, despite the absence of receptors in the retinal blind spot, perception nonetheless occurs and is determined by the characteristics of the immediate surroundings, such as a homogeneous surface or even a line, the latter only if it borders the blind area on both sides. While homogeneous surfaces and simple patterns are readily completed, mildly complex patterns such as a cross may not lend themselves as easily to perceptual completion, but a percept consistent with expectations determined by the visible part can nonetheless be achieved. Implications of this phenomenon for perceptual completion will be discussed later in relation to other examples of completion.

## HALF-OBJECT COMPLETION IN COMMISSUROTOMIZED PATIENTS

The section of forebrain commissures deprives the two cerebral hemispheres of their main means of communication and makes each hemisphere essentially insensitive to the ongoing activity in the other (Sperry, 1982). Given the contralateral representation of each lateral visual field in the hemisphere, each hemisphere is, strictly speaking, blind to the ipsilateral visual field. Although subcortically mediated exchange of information has been demonstrated (Trevarthen and Sperry, 1973; Holtzman, 1984; Sergent, 1986), the consensus is that 'subcortical transmissions are essentially connotational, contextual and orientational in nature' (Myers and Sperry, 1985), and they do not involve the transfer of visual pattern information. In this context, the finding that commissurotomized patients report seeing a complete face when only half a face falls into the visual field projecting to the hemisphere that controls the response (Levy *et al.*, 1972) has been taken as evidence of intrahemispheric perceptual completion (e.g., Trevarthen, 1974). This completion may be consistent with Hebb's (1949) cell assembly theory, whereby part of an object would be sufficient to activate the whole assembly, yet it is not immediately evident how cerebral visual structures, with their retinotopic organization, would mediate the perceptual completion of such a large missing part of the object. An experiment was thus designed that sought to uncover some of the mechanisms mediating perceptual completion in commissurotomized patients, first by attempting a replication of the original finding of Levy *et al.* (1972), then by manipulating stimulus factors susceptible of providing some clues to the underlying mechanisms.

### *Methods*

The experiment was carried out in 1984 on a completely commissurotomized patient (N G.), operated on in 1963 by Drs Vogel and Bogen. The main details of her neurological and surgical history have already been presented (Bogen and Vogel, 1975; Sergent 1986). Bogen *et al.* (1986) have recently reported MRI evidence that N.G.'s forebrain commissures are completely severed, including

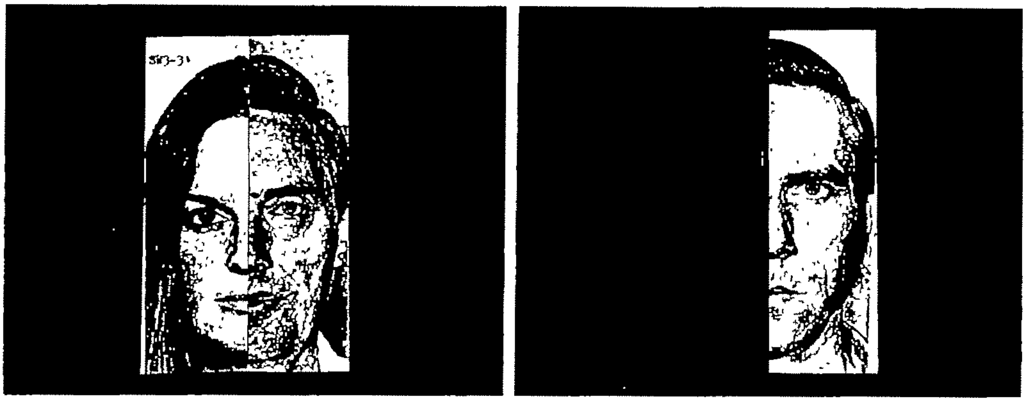

FIG. 2. A chimeric face (A) and a half face (B) used in the evaluation of perceptual completion in commissurotomized and hemianopic patients.

the anterior commissure and the entire corpus callosum. Although N.G. had participated in the study of Levy *et al.* (1972) she had no recollection of it. Another patient (L.B.) participated in the first stage of this experiment but readily said that he was familiar with the task and its purpose, and he was not tested further.

The stimuli consisted of 36 photographs of objects, each appearing in the centre of a black cardboard. Twelve stimuli were front views of full neutral faces (6 men and 6 women); 12 stimuli were made by juxtaposing the left half and the right half of two different faces, along the vertical meridian, such that each half-face appeared in a different visual field and projected to different hemispheres ('chimeric faces', *see* fig 2A; all chimeric faces were made of half a male and half a female face); among the remaining 12 stimuli, 6 were chimeric objects, made of two halves of different instances of the same category, (car, fruit, house) and 6 were made of two halves of objects of different categories (e.g., face-fruit, car-face). The stimuli subtended between 2.5° and 5° of visual angle, and they were presented for 100 ms through a Gerbrands T2-B-1 tachistoscope at a luminance of 5.4 mL on a 0.1 mL background

The 36 stimuli were presented 3 times, each in a different random order. N.G. was told that she would be shown pictures of objects or faces and that she had to look precisely at the dot in the centre of the visual field. In the first two blocks, she was requested to draw exactly what she saw, and she used her right hand in the first half of the first block and the left hand in the second half, while the opposite order was used in the second block. In the third block, N.G. was requested to respond verbally Nothing was said about the nature of the stimuli, but she was told there were male and female faces, as well as cars, houses, and fruits, and that she had to draw exactly what was presented, even if the figures looked unusual. She was repeatedly reminded during the course of the experiment to look very carefully at the central fixation dot once the signal was given. To avoid confusion and interference resulting from the two hemispheres seeing the response sheet, N.G. was not allowed to look at what she was drawing. Although commissurotomized patients are used to this procedure (e.g., Gazzaniga and LeDoux, 1978, Kosslyn *et al.*, 1985), it necessarily results in drawings of poor quality. Nonetheless, N.G. could draw the outline of what she saw and added long or short hair to indicate a female or male face.

## *Results*

The results almost exactly replicated the findings of Levy *et al.* (1972) with this patient. Out of 108 trials, she either drew or reported verbally one complete symmetric object on 101 occasions. The full normal faces were always perceived as such, and she never noticed the double composition of chimeric faces. When N.G. used her left hand, she drew a complete face of the same sex as that falling in her left visual field; when she drew with her right hand, the full face was of the same sex as that falling in her right visual field on 19/24 trials and of that falling in the left field on 5 trials. The verbal response was always a function of the part of the stimulus falling in the right visual field.

Among the 7 instances in which N.G. did not report a complete object, 6 occurred when half a fruit (apple) was associated either with half a car or half a house, in a drawing response with either hand. N.G. then drew a half circle and, after some hesitation, drew a line on the other side. The other instance occurred when N.G. accidentally dropped her response sheet. Except for these 7 trials, in 6 of which the two halves of the chimeric object were quite different in size and brightness, N.G. was essentially unaware of the chimeric nature of the stimuli and she responded that a full normal face or object had been presented.

This finding may be consistent with intrahemispheric generation of the missing half of the object (e.g., Trevarthen, 1974), but one characteristic of stimulus presentation may preclude such an interpretation. Even if only half the object is presented in one visual field, a complete, or at least more extensive, pattern appears, centred on the fixation point, and some information simultaneously reaches the two hemispheres. If the completion of a half object is mediated by cortical processes within one hemisphere, then presenting only half a stimulus in one visual field, just along the midline, should still result in perceptual completion. This was examined in the second part of the experiment.

Twelve new stimuli were thus constructed, each representing only half a face along the vertical meridian, with an equal number of men and women and of left and right visual field presentations, while the other visual field remained black (*see* fig. 2B). The twelve chimeric faces used in the first part of the experiment were also presented, randomly mixed with the half faces, and these stimuli were presented twice, for a total of 48 trials, using the same mode of tachistoscopic presentation as before and requiring a drawing response.

In all cases where a half face was presented, N.G. effectively drew a half face of the appropriate sex, whether it appeared in the right or the left visual field, and whether she used her left or right hand. There was not a single instance of completion of the half face. By contrast, she still drew a complete normal face when presented with a chimeric face, and she was again unaware of the chimeric nature of the stimuli, whereas she readily noticed their unusual nature when these stimuli were later presented in free-viewing conditions.

These observations confirm that a commissurotomized patient perceives a full face when two half faces are presented, one in each visual field. As shown in the second part of the experiment, however, a necessary condition for the perception of a full face from a half face presented in one visual field is the presence, in the other visual field, of some information that may provide clues for filling in the missing half. If the opposite visual field is dark, completion does not occur, and the receiving hemisphere appears to be unable by itself to generate the information necessary for the perception of a whole object. Since there is no callosal connection between the hemispheres of N.G., the only way information from one hemisphere can influence perception by the other is through subcortical pathways. What is considered perceptual completion in commissurotomized patients seems to be the manifestation of subcortical mediation of integrated perception across the visual fields and not the result of some capacity of one hemisphere to produce the missing information.

One question left unanswered by this study is the role of subcortical structures in the integrated perception across the visual fields. Do these structures serve only as a pathway for the exchange of information between the hemispheres, or are the subcortical visual structures capable of encoding and providing the hemispheres with the information about the ipsilateral visual field? An answer to these questions may be provided by the results of an investigation into hemianopic patients in whom cortical visual structures within one hemisphere are destroyed while subcortical structures are not directly affected. Should their performance be similar to that observed in commissurotomized patients, it might suggest a role of subcortical structures in the encoding of information presented in the blind field.

## PERCEPTUAL COMPLETION IN HEMIANOPIC PATIENTS

The first observation of 'perceptual completion' in hemianopic patients was described by Poppelreuter (1917). He observed that some of these patients, when presented tachistoscopically with a figure, part of which fell on the perimetrically blind field, reported seeing an entire figure. This was especially the case with simple figures such as circles or squares, and it could be elicited even when the part of the figure falling in the blind field was omitted. Relatively few investigations into this phenomenon have been conducted since Poppelreuter's original report (Fuchs, 1921; Bender and Teuber, 1946; Pollack *et al.*, 1957; Warrington, 1962; Gassel and Williams, 1963; Torjussen, 1978; *see also* Lashley's (1941) personal experience with the phenomenon in the course of migraine attacks). Because all but one of these investigations have been thoroughly and comprehensively reviewed by Gassel and Williams (1963), they will not be described here.

These investigations have essentially confirmed Poppelreuter's original observation and have established that not all hemianopics display the completion phenomenon. The aim of these studies was thus to determine the conditions under which completion occurs and no general consensus has yet been achieved. Gassel and Williams (1963) pointed out that perceptual completion is the result of a complex of factors. Its occurrence seems to be more likely in patients with mental confusion (Pollack *et al.*, 1957), residual vision (Bender and Teuber, 1946; Torjussen, 1978), poor insight into their visual defect and hemispatial neglect (Gassel and Williams, 1963; Warrington, 1962), and it can be influenced by expectations or mental 'set' (Pollack *et al.*, 1957), the mode of response and the capacity to achieve and maintain accurate fixation (Gassel and Williams, 1963). An important question for the understanding of perceptual completion is then to determine whether these factors directly bear on the phenomenon or whether they introduce confounding effects that set the conditions for the patient's report of a complete perception for reasons other than perceptual completion proper. The experiments to be reported served this purpose.

## EXPERIMENTS

Several reasons may lead a patient to respond that a 'complete' figure was seen, but they may not all relate to perceptual completion. For example, the patient may report the generic term of an incomplete object, or may actually see a complete figure because of residual vision or improper fixation, or may complete the partial figure projected in the intact field. Only the latter qualifies as true perceptual completion, and it is necessary that the investigation be carried out under experimental conditions which minimize the influence of factors that could induce reports of completion that would not be determined by a true process of perceptual completion.

One first requirement is that the patients be able to transmit in a reliable manner the content of their perceptual awareness. One factor potentially interfering with this capacity is concerned with the mental status of the patients and their ability to understand the instructions and to provide accurate reports of what they see. Because these reports *are* the data, patients with mental deterioration or retardation are not appropriate subjects for this type of study that involves no performance measure. The fact that Pollack *et al.* (1957) observed the phenomenon predominantly in mentally deteriorated patients may raise doubts about its existence. If perceptual completion is a genuine phenomenon, leaving aside mentally retarded patients should only guarantee a greater reliability of the data. The present study was therefore conducted with patients who were alert and of at least average intelligence.

Because perception is automatic and directly leads to the awareness of the external world, not in terms of patterns of light but in terms of meaningful objects, the task of describing the actual content of a percept may be rather difficult for the patients. This is especially the case when requiring a verbal response as was done in earlier studies. Such a response taps the later and more abstract stages of perceptual processing and requires an interpretation and recoding of the sensory information into a phonological code from which the particularities of the sensory signals are omitted. A verbal response involves a reduction of the pattern of stimulation to a minimal set of invariants that define a given category and that may be inferred from a partial figure, and it may therefore not be appropriate when one is interested in knowing the physical content of a percept. In earlier studies, the patients were requested to *identify* the figures that were presented, whether or not they were complete, which might have induced them to use the generic term as the closest approximation to what was seen. There is evidence that in identifying visual stimuli, the physical characteristics of the stimuli are processed superficially and quickly decay. For example, when normal subjects are presented tachistoscopically with upper or lower case letters which they have to identify, they accurately report the identity of the letters but cannot provide accurate information about the case of the letters (Friedman, 1980). The fact that perceptual completion was investigated in tasks requiring an identification of the figure and a description of its physical content may have demanded too much of the limited processing resources of the patients who first had to provide the name of the figure. It may also explain why completion typically occurs with figures to which a name is easily attached (Warrington, 1965). This tendency to report a 'complete' figure may be enhanced by the use of familiar, symmetric, and redundant geometric shapes (e.g. circle, square, cross, star) which, as shown by Garner (1974), are highly predictable from a partial view.

To control for these variables in the present study, the patients were requested to produce a drawing response of what was seen, which involves a more direct mapping of the pattern of stimulation onto the descriptive representation of the percept than does a verbal response. To avoid confusion resulting from the natural tendency to give the generic name of a figure even when it is incomplete, some stimuli were included that would bear a different identity when seen as complete or incomplete (e.g. a V or a 3 presented at the border of the intact field would be seen as W or 8 if completed but as V or 3 if not completed).

Another category of factors that may lead to responses of 'complete' figures that would be improperly attributed to perceptual completion concerns the possibility of actual perception in the affected field. Several authors have attributed perceptual completion to residual vision, either as the sole explanation (Bender and Teuber, 1946) or as one of the contributing factors (Gassel and Williams, 1963; Torjussen, 1978). As noted by Gassel and Williams (1963), 'the extent to which there is retention of vision is the extent to which the term 'completion' is inapplicable' and it is therefore necessary to examine completion in patients with dense homonymous hemianopia. Also of critical importance is the presence of macular sparing. Because stimulus presentation takes place in the centre of the visual field, macular sparing in the hemianopic field would allow perception in both fields of presentation. In the present experiment, only patients with macular splitting were selected.

A last source of confusion in the evaluation of perceptual completion is eye fixation. Due to their visual field defect, the area of highest acuity normally used for fixation is just at the border of the blind field, which is not convenient to focus on a target. To compensate for their defect, hemianopic patients tend to deviate their visual axis towards the hemianopic field so that the focus of their attention is surrounded by an area of vision. It is therefore difficult to determine where a hemianopic patient is fixating and, as noted by Williams and Gassel (1962), 'we are unable to assume fixed central direction of the visual axis when the patient is asked to look straight at a fixation target in a visual fields examination' (p. 221).

No eye-movement recording device was available for this investigation, and several procedures were devised to examine where in the visual field the patients are naturally fixating when requested to look straight ahead, and to introduce a means of controlling for eye fixation.

Each of the identified potential sources of confusion in the evaluation of perceptual completion was thus controlled in this study. Other factors thought to contribute to some extent to the phenomenon, such as parietal lobe disease (Warrington, 1962), hemispatial neglect and unawareness of the field defect (Gassel and Williams, 1963) and brief stimulus presentation (Bender and Teuber, 1946) were not considered as interfering with the evaluation of the phenomenon and were included as independent variables in this study. Each patient was subjected to several tasks run on consecutive days over a period of at least two weeks.

### *General methods*

All the tasks were conducted through a Gerbrands T3-B-1 tachistoscope. The subject sat in front of the tachistoscope, the forehead resting on a support that presented head movement and that could be adjusted so that the eyes were just at the level of the fixation point in the centre of the visual field which subtended 10° in width and 7.1° in height. Viewing was binocular. The subjects were tested in sessions of 30 min that could be shortened or extended depending on the patient's level of fatigue and concentration, or at his or her request.

### *Subjects*

Selection of the patients was based on the ophthalmologist's report of dense homonymous hemianopia and macular splitting tested by confrontation and perimetry with coloured and white targets, on evidence of at least average intelligence, and on the patient's consent to participate in an extensive tachistoscopic study for research purpose. All patients were right handed, as assessed with Oldfield's (1971) questionnaire, and had a full scale IQ of at least 102 on the WAIS. Density of hemianopia was further examined through lateral tachistoscopic presentation of bright patterns (15 mL) on a dark background, and only 1 patient (Case 2) showed evidence of residual vision in the affected field.

*Case 1.* This 28-year-old woman's first symptoms occurred in 1981 when she suffered a generalized seizure after experiencing flashing lights in her left visual field. A CT scan revealed a right occipital lesion. A right occipital astrocytoma-oligodendroglioma was removed in February 1982, resulting in a dense homonymous hemianopia with macular splitting. She has had no noticeable seizure since the operation, and a CT scan conducted in May 1986 showed no evidence of recurrence of the lesion. She has resumed her work as an accounting clerk. Her Snellen acuity is 20/20, and she displays no evidence of attentional neglect on drawings, line bisection and line crossing. She is aware of her field defect but still bumps into objects on her left.

*Case 2.* This 73-year-old businessman was admitted in March 1986 after onset of right-sided visual problems and confusion the previous day. Neurological examination showed a right homonymous hemianopia without macular sparing, and difficulty with his gait without weakness on either side. A CT scan revealed evidence of intracerebral haematoma involving the left parietal and occipital areas, probably the consequence of congophilic arteriopathy. He was mildly confused, alexic and dysgraphic, occasionally anomic, and he displayed a strong right visual neglect evidenced on formal testing. Confusion and verbal symptoms improved within a month, and a CT scan one month after admission showed diminishing amount of blood in the haematoma. Hemianopia and visual neglect persisted, and he was unaware of his field defect but did not deny it on demonstration. However, he could report the appearance of light in his hemianopic field but could not identify patterns Snellen acuity was 20/20 with his glasses. He had no difficulty copying drawings with his left hand before testing.

*Case 3.* This 69-year-old man was admitted after experiencing difficulties in reading. He had a dense right homonymous hemianopia and macular splitting on perimetry, but normal eye movements. Snellen acuity was 20/25. MRI suggested a space-occupying lesion in the left occipital lobe and the posterior part of the parietal lobe. There was evidence of slight right visual neglect on formal testing, and he was not aware of his field defect. He had no difficulty reading briefly flashed letters in his intact field.

*Case 4* This 49-year-old civil servant woman was admitted in April 1986 with a history of left hemiparesis for 2 wks before admission, preceded by headaches She had a dense left homonymous hemianopia with macular splitting. She was mildly confused, with slow speech, but no evidence of dysphasia. A CT scan revealed a large high grade glioma in the right temporoparietal region which was removed 2 days after admission. There were no operative complications and her mental state improved, except for a slight visual neglect on the left. Her Snellen acuity was 20/30. She was cooperative on testing for 10 consecutive days, but her mental state started to deteriorate, and she was tested on only one additional session afterwards

*Case 5.* This 34-year-old architect underwent resection of a right parieto-occipital oligodendroglioma in 1982, which resulted in a left inferior quadrantanopia. He was readmitted in May 1986 for episodes of headaches, vomiting, and nausea. A CT scan showed evidence of tumour recurrence in the right occipital region, and he underwent a complete right occipital lobectomy. His condition was improved but he was left with a dense left homonymous hemianopia with macular splitting. Snellen acuity was 20/25, and he had no deficit of eye movements. He was aware of his field defect and his performance on tests of visual neglect was within normal limits.

*Case 6.* This 57-year-old woman was well until December 1985 when she experienced a short episode of disorientation. She was admitted in April 1986 for examination which revealed a dense homonymous hemianopia without macular splitting. A CT scan revealed a large space-occupying lesion in the right temporoparietal region, and she was operated on for removal of the tumour which originated from the tentorium. No added neurological deficit resulted from the operation, but she displayed visual neglect to her left on formal testing. Her corrected Snellen acuity was 20/20 and she was unaware of her field defect.

## *Preliminary control tasks*

### *Task 1. Examination of 'straight ahead'*

Eye deviation towards the hemianopic field (Gassel and Williams, 1963) makes testing difficult in conditions where accuracy of fixation is critical to the evaluation. To assess the extent of eye deviation in each patient without oculography, a behavioural method through tachistoscopic presentation was devised. It consisted first of measuring Snellen acuity, then in constructing cards on which rows of single letters or digits of a size corresponding to the Snellen acuity of the patient were printed. These cards were then presented tachistoscopically to the patient who was requested to look at a central fixation point and to identify the letters or digits. The rationale of this method is that Snellen acuity corresponds to the resolving power of the foveal retinal area; by requesting the patient to look straight ahead and by presenting, on the horizontal meridian, several single letters or digits of a size that only the foveal area is capable of resolving, the location of the identified alphanumeric character with respect to the centre of the visual field would indicate where the patient is actually fixating.

*Methods.* Snellen acuity was initially available from the ophthalmologist's report and was measured again on 2 additional occasions before the task. Twenty stimulus cards were prepared, each containing 9 single alphanumeric characters, 1° of visual angle apart along the horizontal meridian, 1 in the centre of the visual field and 4 on each side. The central character was displaced 0.25° from the actual centre towards the intact field to avoid its falling on the vertical meridian. The size of the characters depended on each patient's Snellen acuity and was prorated as a function of the viewing distance in the tachistoscope.

The letters were Letraset Futura Medium and appeared in black on a 15-mL white background. The preexposure and postexposure fields were dark and contained a bright white dot, 0.33° of visual angle, located exactly in the centre of the visual field. Each card was presented for a duration of 120 ms. The subjects were initially shown what tachistoscopic presentation looked like with 10 blank trials and then 10 trials with letters.

The patients were requested to look straight ahead at the central white dot and to keep fixating it until after the stimulus card had been presented. They were told that they would be shown letters or digits and that their task was to report those they could identify. It was also mentioned that they should report more than one if they had identified two or more, but that most people see only one. Ten normal subjects were also tested on this task, using the same procedure. In their case, the central letter was displaced towards the right in 10 trials and towards the left in the other 10 trials.

*Results.* In 3 patients (Cases 1, 2, and 5), the size of the letter had to be increased after 10 trials as they had not been able to report more than 5 characters. This presumably reflected a deficit in the temporal integration of luminous energy frequently observed in posterior brain-damaged patients (e.g., Ettlinger, 1956; Rosenthal and Fedio, 1975). For all patients, cards to which no response was given were repeated later in the sequence, and such a failure to respond occurred on an average of 4.2 trials.

Deviation of the eyes towards the blind field was observed in all patients, and the mean deviation across subjects was 2.5° (ranging from 0.9° to 3.6°). Case 1 displayed the least eye deviation (0.9°) and identified the central character in 4 out of 20 trials. None of the other patients could identify the central character, and the letters and digits they reported were those located between 1° and 3° from the central dot on 92% of the trials. No such deviation was observed in the normal subjects.

These results confirm that hemianopics, regardless of the side of the lesion, are unable to look straight ahead when requested to fixate a target in the visual field and deviate their gaze towards the hemianopic field. Bender and Teuber (1946) also reported eye deviation of about 3° in hemianopic patients during the course of testing perceptual completion. This failure to achieve accurate fixation without the patient's awareness has important practical implications for the study of perceptual completion as it suggests that the patients may see more of the stimulus than is usually assumed.

### *Task 2. Guiding eye fixation*

One way of overcoming eccentric fixation was to provide the patients with landmarks that would guide them in fixating as intended. For this purpose, the preexposure field was divided into two parts: one lateral half was coloured in pale blue and the other in pale green (Letraset Pantone 227-M and 365-M, respectively, both of the same reflectance), the division falling exactly on the vertical meridian and splitting the central fixation point (no line other than the junction between the two colours separated the two halves of the card). In addition, at the top and bottom of the visual field (3° from fixation), a small black square (0.5° of visual angle) was located within the intact field, the inner side falling just on the vertical meridian. With this arrangement, the patients were requested to fixate the central dot in such a manner that they would see only the blue (or green) surface and that they see one square at the top and one square at the bottom.

To test the efficacy of this method, each patient was tested again with the same stimuli as in Task 1, after measuring their Snellen acuity to control for letter size. The only difference with Task 1 was the 2-coloured pre- and postexposure field. Five patients reported the central alphanumeric character on all 20 trials while Case 3 did so on 16 trials and reported the character located 1° from fixation within his intact field on 4 trials. The 2-coloured preexposure field was thus efficient at guiding patients in fixating the central dot, and this method provides a simple and straightforward way of controlling eye fixation in hemianopic patients, to the extent that they are cooperative.

## *Perceptual completion tasks*

### *Task 3. Main completion task*

This task was the critical experiment of this series and aimed at examining perceptual completion under tighter control than had previously been done. The 2-coloured preexposure field was used for guiding fixation and the subjects responded by drawing what they saw using the hand ipsilateral to their lesion. No specific instruction was given regarding the quality of drawing, except that they were asked to draw exactly what was seen.

*Methods.* There were 80 stimuli in all, a sample of which is shown in fig. 3. They comprised 14 faces (4 full, 4 chimeric, and 6 half faces, *see* fig. 2), 32 symmetric geometric shapes (circle, square, oblong, and star, each appearing equally often as line-drawing or filled, complete or partial, as black on white or as white on black), 2 letters (X, M) appearing in the centre and 1 letter (V) and 1 digit (3) appearing in the intact field (the latter 4 appearing either as black or as white), 4 symmetric complex patterns, and 6 pictures of various symmetric objects (monuments, cars, fruit). These 64 stimuli appeared in the centre of the visual field when complete or along the vertical meridian in the intact visual field. In addition, 16 of these stimuli were also presented laterally, 8 entirely within the right visual field and 8 within the left visual field, with the inner edge 1° from the centre. The stimuli subtended between 2° and 4° of visual angle. The same cards were used for all patients, but were placed in different channels of the tachistoscope depending on the side of the patient's blind field. The 80 stimuli were presented 3 times, on different days, successively at exposure duration of 50, 100, and 150 ms. To control for accurate fixation during the course of the experiment, the alphanumeric stimuli used in Task 1 were presented at random intervals without specific warning and the patient was asked which letter or digit he or she had identified.

The stimuli were presented in a different random order for each patient, except for the first three presentations which always occurred entirely within the patient's intact field and which comprised a

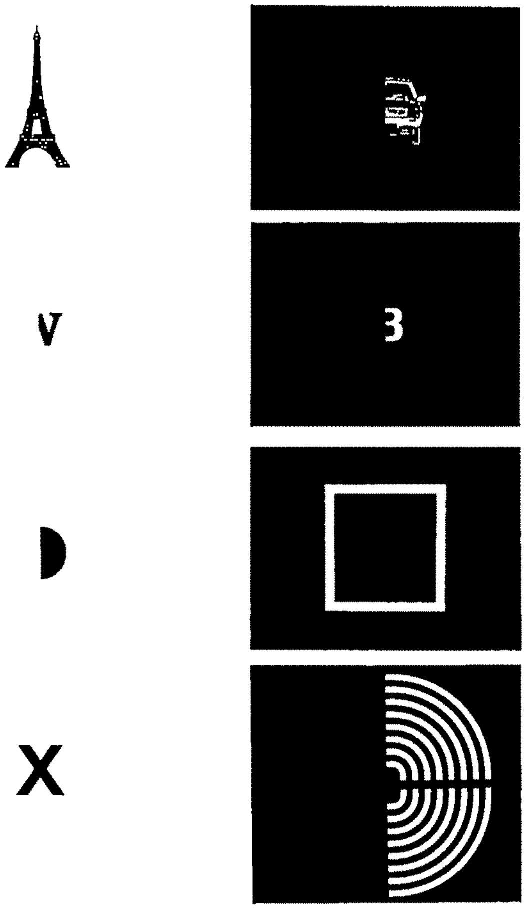

FIG 3 Sample of the stimuli used in the evaluation of perceptual completion in hemianopic patients

complete square, the left half of a male face, the right two-thirds of a filled circle, as well as a fourth presentation consisting of a blank trial. These served the purpose of ensuring that the patient understood the instructions and could reproduce what was seen in conditions independent of the completion phenomenon. All patients accurately reproduced what was presented in their intact field, and understood that there would be trials where they might see nothing. The experiment was run at a slow pace, and the patient was reminded, before each trial, to look at the central dot such that only one colour was seen along with the two squares at the top and bottom of the visual field.

*Results.* The results were unexpectedly straightforward for 4 of the patients (Cases, 1, 3, 5, 6). On all trials, and at each exposure duration, they reproduced exactly what could be perceived objectively given their hemianopia. There was no instance of perceptual completion, and they never drew the part of the figure that fell in their blind field. The patients were accurate in reporting the alphanumeric character the closest from fixation in the control trials, suggesting that, as a rule, they were capable of sustaining accurate fixation and that their blind field fell as intended along the vertical meridian. There was no evidence that they were aware that the complete figures appearing in the centre of the visual field extended beyond the vertical meridian, and there was no difference in their responses to partial and complete figures. They accurately reproduced the figures appearing in their intact visual field, and they reported seeing nothing on those trials where the figure was entirely projected to their blind field.

Case 2 showed a different pattern of results, and he produced 32 responses that could be taken as evidence of perceptual completion (*see* Table 1). Of these responses, 23 occurred at 50 ms exposure, while 5 and 4 occurred at 100 and 150 ms, respectively. Of these 32 responses, 25 consisted in drawing a complete geometric figure or letter when a complete figure was actually presented, while 7 occurred after presentation of incomplete figures appearing as black on a white background. The patient often volunteered the information that he was not sure of his response but that he had the feeling that he had seen a complete figure. That residual vision in his blind field, demonstrated in initial testing, may have contributed to these responses is suggested by the fact that, in 6 out of 24 trials in which a stimulus was entirely presented in his right hemianopic field, he was aware that something had appeared and drew a circular shape. This occurred only with white filled geometric figures but not with line drawings of these figures, in the absence of stimulation in the intact field.

TABLE 1 NUMBER OF FIGURES REPORTED IN THE AFFECTED FIELD AND DISTRIBUTION OF 'COMPLETE' RESPONSES TO COMPLETE AND TO PARTIAL FIGURES, AS A FUNCTION OF EXPOSURE DURATION, BY CASE 2 (TASK 3)

| | *Exposure duration (ms)* | | |
|---|---|---|---|
| | *50* | *100* | *150* |
| Report in blind field (out of 8 per exposure) | 4 | 2 | 0 |
| 'Complete' responses to | | | |
| Complete figures (out of 40 per exposure) | 20 | 3 | 2 |
| Partial figures (out of 24 per exposure) | 3 | 2 | 2 |

Case 4 displayed the same type of results as the first 4 patients in the two first sessions, and she drew a figure as a function of what could be seen objectively, given her hemianopia. Her condition started to deteriorate after the second session, but she was still cooperative and willing to participate in the study. In the last session, all the simple and familiar figures presented in the centre, either full or partial, were reproduced as complete, and she verbally described as complete the more complex figures which she was not able to draw. This was also the case for shapes appearing in her intact field. The only exceptions to 'complete' reports were her responses to the letters and digits which were always based on the part falling in her intact field.

Overall, these results are not entirely consistent with the view that hemianopics can fill in the missing information when only part of the figure is presented in the intact field, and the patients displaying responses suggestive of completion had either evidence of residual vision in the affected field or mental deterioration. These findings might then suggest that earlier demonstrations of perceptual completion were due to a combination of factors that induced the patients to respond that they were seeing a complete figure for reasons other than completion as such. However, the present failure to disprove the null hypothesis of absence of completion must be regarded with caution because, in earlier studies, perceptual completion was not observed in all patients, and it is possible that the patients participating in the present experiment fell into the category of patients not prone to completion.

### *Task 4. Completion with verbal response and uncontrolled fixation*

The purpose of Task 4 was to place the patients in conditions more like those prevailing in earlier studies in order to determine whether the null finding of Task 3 was attributable to the patients themselves or to the tighter procedural controls. The same 80 stimuli were presented at 50 ms, using the same procedure as before with two exceptions: the 2-coloured preexposure field was replaced by an entirely green field with a fixation dot in its centre, thus eliminating the guide for accurate fixation; the patients were required to provide a verbal instead of a drawing response. Ten stimulus cards with 9 alphanumeric characters (*see* Task 1) were also presented at random intervals to determine the locus of fixation.

*Results.* The results of this task are summarized in Table 2. Eccentric fixation was evidenced by the patient's identification of alphanumeric characters falling in the hemianopic field, as had already been observed in Task 1. In addition, among the 80 stimuli, 8 were presented entirely in the affected field, and 3 patients consistently reported their presence, in sharp contrast with the finding of Task 3 in which the landmarks to guide fixation had prevented such reports. In the initial 3 trials, 3 patients had to be corrected when responding to the partial stimuli appearing in their intact field, as they reported 'a man's face' and 'a circle' when half a face and two-thirds of a circle were actually presented. They justified their responses by saying that half a face does not make sense, or that they could see that only a small part of the circle was missing, but that they thought that they

TABLE 2 EYE DEVIATION (IN DEGS), NUMBER OF FIGURES PERCEIVED IN THE AFFECTED FIELD, AND DISTRIBUTION OF 'COMPLETE' VERBAL RESPONSES IN THE ABSENCE OF CONTROL OVER FIXATION (TASK 4)

| | *Case* | | | | |
|---|---|---|---|---|---|
| | *1* | *3* | *5* | *6* | |
| Eye deviation | 0 3 | 2 4 | 3 1 | 1 9 | |
| Responses in blind field (out of 8) | 2 | 6 | 7 | 7 | |
| 'Complete' forms reported (out of 64) | 6 | 33 | 28 | 21 | 34% |
| Complete stimuli (40) | 4 | 24 | 21 | 16 | 41% |
| Partial black stimuli (12) | 2 | 8 | 7 | 5 | 46% |
| Partial white stimuli (12) | 0 | 1 | 0 | 0 | 2% |

had to tell what object it was. The patients were therefore asked to qualify their response by saying 'complete' or 'incomplete' in addition to identifying the object.

The total number of responses suggesting perceptual completion is shown in Table 2, for each patient. Overall, the patients responded seeing a 'complete' form on 34% of the trials, of which 74% were to complete stimuli and 26% to incomplete stimuli. There was a significant correlation between the extent of eccentric fixation and the number of 'complete' reponses to objectively complete stimuli ($r=0.92$, $P<0.01$). Incomplete stimuli yielded a different pattern of responses depending on whether they appeared as black on a white background or as white on a black background. As shown in Table 2, the former yielded approximately the same proportion of 'complete' responses (46%) as did complete stimuli (41%) while the latter elicited only 1 'complete' response (2%). These two types of partial stimuli were the positive and negative representations of the same figure, and this difference proved critical in the perception of a pattern as complete or incomplete.

The important result of Task 4 is that patients who displayed no evidence of perceptual completion when fixation was controlled and a drawing response was requested produced responses suggestive of perceptual completion when these critical variables were not controlled. This suggests that the null result of Task 3 cannot be due to the patients themselves. It is noteworthy that Case 1, who showed the least eye deviation and had no detectable damage to the parietal lobe, displayed very few instances of perceptual completion, and she may be representative of those patients who, in previous studies, failed to complete figures with a segment falling in their blind field.

### *Task 5. Completion with verbal response and guided fixation*

A final task was conducted in an attempt to examine the influence of a verbal response on the results of Task 4 while controlling the fixation. The same 4 patients were presented with 40 stimuli (32 geometric shapes and letters and digits used in the two preceding tasks), in exactly the same conditions as in Task 4 with one exception: the 2-coloured preexposure field was now used for guiding fixation and a verbal response was still requested, with the qualification of 'complete' or 'incomplete' for each response. Case 1 always reported the geometric shapes as 'incomplete', while Cases 3, 5, and 6 had 9, 12, and 9 instances, respectively, of 'complete' responses with these shapes, always with black figures on a white background. When queried about these responses, they said they were not sure and could not tell with confidence whether or not they were complete, but Case 5 mentioned that the figures were most likely complete because he had no difficulty seeing what they were. However, there was no instance of 'complete' response with white figures, even though they were correctly identified, and the patients reported that it was easy to see that they were cut while it was difficult to determine whether a black figure was cut or complete.

Of particular interest in this respect were the responses to the letters and digits. For example, when a white X was presented in the centre, it was reported as a tilted V, but when a black X was presented in the centre, it was reported as K. This suggests that the border of the blind field was used as the vertical bar to add some information to the black letter, but not to the white letter. In contrast to the geometric shapes, the patients had no hesitation responding to the letters and digits, and their responses were always based on the part falling in their intact field. For instance, a white M was seen as 1 and a black M was seen as N by the patients with left hemianopia, while the V and 3 were seen as N and B when black, and as V and 3 when white, with no evidence of completion into W or 8.

### *Comment*

The results of this study indicate that the occurrence of perceptual completion in hemianopic patients is influenced by a series of factors that may induce reports of complete perception, not all of which are related to a true process of perceptual completion. It is thus necessary to identify which factors contribute to the particular outcomes and to examine the source of the disparity between the present results and earlier findings.

*The experimental task.* In the investigation into perceptual completion, in which the data are the patients' reports about their perceptual experience rather than objective measures of performance, reliable observations are difficult to obtain because of the nature of the phenomenon: perception is aimed at objects, not at patterns of light, yet it is the latter to which perceptual completion refers and of which the patients must report their perceptual awareness. Pollack *et al.* (1957) found that perceptual completion occurred predominantly in mentally deteriorated patients, casting doubts on the existence of a *perceptual* phenomenon that could not be demonstrated in patients of at least average intelligence. The exclusion of deteriorated patients in the present study received justification from the unexpected deterioration of Case 4. While she showed no evidence of completion in the first two sessions of Task 3, she repeatedly reported seeing a 'complete' figure in the last session, even after being shown the half figure to be presented. This finding concurs with the observation of Gassel and Williams (1963) of the greater occurrence of completion with mental confusion, and suggests that this factor may have contributed to earlier demonstrations of completion. It is also noteworthy that the patients participating in Tasks 4 and 5, all alert and of at least average intelligence, were spontaneously inclined to report verbally the *object* they were perceiving rather than the *pattern of light*, even though they had been accustomed to the latter in Task 3.

In previous studies, the completion phenomenon was investigated by requesting patients to *identify* the figure in addition to describing the pattern of light. Such an identification, indexed by a verbal response, requires the extraction of the invariants that uniquely define a given category, and it may leave little processing resources to attend to the particularities of the stimulus. As illustrated in Tasks 4 and 5, there were several instances of 'complete' responses in which the patients were unaware of the actual physical content of the stimulus, a finding similar to that observed in normal subjects (Friedman, 1980). In particular, Task 5, which differed from Task 3 only by the use of a verbal instead of a drawing response, offered some evidence that a verbal mode of response contributed to reports of complete perception. The greater incidence of completion with figures to which a name can be attached (Warrington, 1965) may then partly result from the verbal identification which is based on a code that no longer contains information about the exact content of the stimulus. That it is the verbal response as such, not the availability of a name, that contributes to 'complete' responses is suggested by the fact that the same stimuli yielded instances of completion with a verbal (Task 5), but not with a drawing (Task 3) response. There is therefore reason to doubt the purely *perceptual* mediation of a phenomenon, the occurrence of which would depend on the involvement of verbal processes.

This is not to suggest that the particular choice of the stimuli has no influence on the outcome. In most investigations, symmetric, well known, and redundant figures were presented. Such stimuli have the characteristic that they are highly predictable from a partial view and have therefore very few degrees of freedom. In addition to being amenable to verbalization, these stimuli leave little doubt as to their identity when incomplete, and even a partial view contains the invariants required for accurate identification. Moreover, the use of such stimuli precludes an objective mean of determining whether they are seen as 'complete' or 'incomplete' as the same name applies to both versions. To overcome this difficulty, stimuli were included that bore a different identity when seen as complete and incomplete, thus offering a more objective way of telling how much of the stimulus was really seen by the patient. In the two tasks where eye fixation was guided (Tasks 3 and 5), the response to these stimuli was always determined by the part of the figure falling in the intact field and no evidence of completion was found, even though these stimuli shared with geometric figures the property of symmetry and familiarity, but not that of redundancy. It is of interest to note that this was also true for Case 4 even after her mental state had started deteriorating.

A last procedural factor found to contribute to the completion phenomenon concerns the respective luminance of the figure and the ground. Except on one occasion in Task 4, there was no report of a 'complete' figure with white stimuli appearing on a black background. In such a condition, both the hemianopic and the intact field background are deprived of luminous energy, and the only source of stimulation is provided by the figure itself. The patients then reported seeing only that part of the figure falling in the intact field, and what was seen was directly and uniquely determined by the stimulation of functional visual areas and did not extend to the blind field. By contrast, black figures on a white background resulted in 'complete' responses on several occasions, and nearly all instances of perceptual completion occurred with such figures. To the visual system, these figures are, strictly speaking, defined by an absence of stimulation on a stimulated field, and their extremities blend with the blind field, leaving no precise clue as to where they actually end. There is therefore an important difference between the two types of figure-ground arrangement which turned out to be of significance in the occurrence of 'complete' responses. The exclusive use of black figures in earlier studies may have contributed to reports of completion that would have not have occurred with white figures.

The foregoing considerations suggest that the experimental task to which the patients are subjected for the evaluation of the perceptual completion phenomenon inherently contains a variety of factors susceptible of inducing responses of completion without the patients necessarily seeing the missing information. The nature of perception itself, the intrinsic difficulty in attending to the pattern of light rather than to the object as such, the properties and characteristics of the stimuli, all these factors converge towards favouring reports of complete perception. The inclusion of stringent operational criteria in the present investigation was thus justified to ensure that these factors would not be at play in the assessment of the phenomenon.

*Factors associated with visual function in hemianopia.* It was noted by Gassel and Williams (1963) that residual vision in the hemianopic field and eccentric fixation significantly contributed to reports of 'complete' figures, and this was confirmed here. Although all the patients were described as having dense homonymous hemianopia, Case 2 reported seeing a circular shape when a filled geometric figure was flashed in the hemianopic field in the absence of stimulation in the intact field. Thus there was some residual vision in the affected field of this patient, but it was very crude and did not permit identification of any of the shapes presented in this field. Yet he produced a total of 32 'complete' responses by which he indicated that he could see the part of the stimulus falling in the blind field (not simply a circular shape), suggesting that concurrent stimulation of the intact field enhanced the response to stimulation of the affected field. This was the case with filled symmetric figures, especially at very brief exposure, and it indicates that completion can occur under some conditions and lead to perception in the affected field which is achieved with a greater distinctness of the figure that can be obtained by stimulating that field alone. Torjussen (1978) also reported findings suggesting that completion could occur as a result of an interaction between the stimulated areas of both sides of the vertical midline. He proposed that concurrent stimulation of the intact field facilitated the detection of the stimulus portion falling in the hemianopic field, at least with symmetric figures. While the results for Case 2 confirm Torjussen's findings, none of the other patients produced responses suggestive of such a process.

Eccentric fixation towards the hemianopic field was observed in all patients to some extent, as assessed in Tasks 1 and 4. The patients were unaware of this eye deviation which appears to reflect an adaptation to the restricted field of vision so as to position the target within a surrounding context. It was found irrespective of hemispatial neglect but was more pronounced in patients with parietal lobe damage, perhaps as a result of destruction of structures contributing to gaze fixation and eye movement (Hyvärinen, 1982). The results of Task 2, in which landmarks were provided for guiding eye fixation, indicated that the patients could achieve and sustain accurate fixation, and the 'surprise' trials in Task 3 confirmed that they were looking as intended during the evaluation of perceptual completion. That eccentric fixation significantly contributed to responses of 'complete' figures was indicated by the significant correlation between the extent of eye deviation and the incidence of 'complete' responses (Task 4). This does not explain the entire results, however, and it did not systematically lead to completion. Nonetheless, an examination of individual 'complete' responses indicated that they were more likely to occur with figures subtending a small degree of visual angle, thus within the extent of eye deviation.

While the present results provide limited support for the existence of perceptual completion in hemianopics, as assessed in Task 3, they do not explain the variability across patients in the incidence of 'complete' responses in Tasks 4 and 5. None of the identified experimental factors was sufficient by itself consistently to determine reports of complete figures and all patients had at least some instances of completion while none had a 100% incidence (except Case 4 in her last session). Warrington (1962) suggested that damage to the parietal lobe was necessary for the occurrence of completion, and the present results showed a similar trend in that Case 1 (the only one whose lesion did not invade the parietal lobe) displayed the smallest number of 'complete' responses. It is possible that hemispatial neglect, which is often associated with parietal lobe damage (Bisiach and Berti, 1987), was responsible for the absence of 'complete' response in Task 3. The patients might have, in fact, completed the figures and seen the missing part in their affected field, but, because of their hemineglect, they drew only half of the figures. The use of a drawing response would thus have created a confounding factor and would not provide a valid method for the examination of the true *perception* of the patients, whereas a verbal response would be less vulnerable to the influence of hemineglect.

There are several reasons to believe that the use of a drawing response did not prevent the patients from reporting what they were seeing. First, Case 2, who suffered from visual neglect at the time of testing, did produce drawings of complete figures while Case 5, who had parietal damage but no evidence of hemineglect, did not produce 'complete' responses with a drawing response but did so with a verbal response. Thus hemineglect did not prevent 'complete' drawing responses and the absence of neglect was accompanied by a failure to report the missing half of the figure. Secondly, given that hemispatial neglect affects the perception of one half of objects even within the nonaffected hemispace (e.g., Bisiach and Berti, 1987), the patients should have neglected half of the figures entirely presented in the intact field, but they did not and produced complete drawings of the figures in this condition. Thirdly, all the patients could copy complete geometric figures or draw them on request; even when they displayed evidence of neglect in drawing a clock, they always drew a full circle and only the digits inside the circle were misplaced. It thus seems warranted to suggest that, when the patients drew a half figure in Task 3, it was not because they were neglecting or could not draw the other half but because they did not see it. Other factors associated with parietal damage may explain the greater incidence of completion in parietal patients. For example, it may be due to the fact that these patients, compared with either occipital or temporal patients, show a greater difficulty fixating a target (Hyvärinen, 1982) due to unawareness of the field defect and denial of illness, have a higher frequency of residual vision (Harrington, 1981) and a higher incidence of mental deterioration (Critchley, 1953). In this sense, parietal damage may result in conditions which, in conjunction with the use of a verbal response and familiar and simple stimuli, contribute to the production of 'complete' responses for reasons other than a true process of completion.

## DISCUSSION

This study was designed to investigate the conditions favouring the occurrence of perceptual completion in three different situations. The demonstration of vision over the retinal blind spot qualified as a genuine perceptual completion, but the suggestion of intrahemispheric completion in commissurotomized patients was not confirmed and only limited support was found for completion in the blind visual field of hemianopic patients. While keeping in mind Teuber's dictum that 'absence of evidence is not evidence of absence', the main conclusion of this investigation is that perceptual completion does occur but all reports of completion are not due to the subjects seeing more than is objectively available.

Considering first the negative findings obtained with the commissurotomized and hemianopic patients, it appears that the experimental conditions prevailing in the examination of the phenomenon were found to play a determining role in the production of 'complete' responses and they could be set in such a way as to eliminate the occurrence of these responses in all but one patient. In addition, behavioural deficits associated with parietal lobe disease, such as mental deterioration or confusion, unawareness of field defect, inaccurate fixation, may interact with experimental variables and lead to a greater incidence of 'complete' responses. When these factors were controlled or excluded, most patients reported seeing no more than would be predicted from the perimetric mapping of their visual field. In the 5 patients with dense homonymous hemianopia, conjoint stimulation of both fields did not enhance perception in the affected field as it did in Case 2 who displayed some residual vision. This may indicate that completion, when it occurs, is unlikely to result from the intact cortical areas generating the missing information, and the commissurotomized patient's responses to half-object presentations also suggest that the stimulation of one hemisphere cannot produce perception over both visual fields.

On the other hand, the results in Case 2 provide some evidence of perceptual completion, in the sense that he could see more in his affected field when both fields were stimulated than would be predicted by stimulation of the affected field alone. Although the source of his residual vision cannot be specified, earlier findings by Torjussen (1978) in patients showing no signs of residual vision but evidence of perceptual completion suggest that the involvement of subcortical visual structures may underlie this completion process. The role of these structures in some visual processes is now well documented (Weiskrantz, 1986) and they may subserve the generation of the missing information when the intact field is conjointly stimulated, at least with simple, symmetric figures (Torjussen, 1978). These structures are nonetheless limited with respect to the complexity of the visual information they can mediate and bring to perceptual experience (Weiskrantz, 1986), and this may explain why Case 2 never completed the complex figures such as faces and monuments that were part of the stimulus set. This may also provide an answer to the question raised by the results of half-object completion in the commissurotomized patients (p. 108). The report of a full face when either a chimeric or a complete face was presented resulted from an integration of perceptual experience through subcortical structures serving as pathways between the two hemispheres and not from these structures generating the ipsilateral information.

The simplest, and most convincing, demonstration of perceptual completion was the filling in of the blind spot in accordance with the immediate surroundings, as illustrated in fig. 1A. There, the blind area is 'invaded' by the adjacent pattern of stimulation such that a homogeneous field is seen. This is a robust phenomenon and the 4 hemianopic patients who participated in Tasks 4 and 5 were also asked to describe what they were seeing on each of the three demonstrations presented in fig. 1, using three separate green cards. Each patient's description was qualitatively similar to that of normal subjects, and the blind spot was reported as being filled with a green surface similar to the immediate neighbourhood. The patients having experienced what perceptual completion actually is, they were then requested to look at the centre of the 2-coloured card as they had done in the earlier tasks, such that they see only one colour along with the two squares bordering the visual meridian, and they were asked whether they could see that colour beyond the fixation point and the two squares. For each patient, the vision of that colour stopped right at the vertical meridian, and there was no report that the immediate border invaded the blind field, not even the part adjacent to the intact field. This constitutes evidence against perceptual completion in the hemianopic field which would result from stimulation of the intact field alone. If there were completion in the hemianopic field as there is in the blind spot, the most straightforward evidence of completion in the blind spot should be manifest as well in the hemianopic field, but this was not the case (neither monocularly nor binocularly).

This raises questions about the similarity of perceptual completion in the blind spot and the hemianopic field, and they deserve consideration since Poppelreuter (1917) and Gassel and Williams (1963) suggested that 'the hemianopic defect functions as an extended blind spot.' Several differences between these two blind areas are worth pointing out. One is directly related to the nature of hemianopia which results from cerebral damage and is generally only one of the symptoms observed in hemianopic patients. As noted earlier, associated deficits may contribute to performance in tasks aimed at investigating perceptual completion. Other differences are essentially structural.

The blind spot is located 15° from fixation where acuity is about 10% what it is in the centre of the visual field, whereas completion in hemianopic patients is tested along the vertical meridian in a retinal area of high acuity. A missing segment in a figure may be less conspicuous in a peripheral part of the visual field which is not normally the focus of attention than in the centre of the visual field. In addition, the blind spot subtends a relatively small area entirely surrounded by an intact and functional area of vision, whereas hemianopia affects a large part of the visual field and is bordered only on one side by an intact visual field, represented cortically in the other hemisphere. If the immediate surroundings of a blind area determine perceptual completion (and, as suggested by fig. 1c, the presence of a line on both sides of the blind spot is required for completion), then completion may be less likely in the hemianopic field than in the blind spot. It is also the case that demonstration of the blind spot, and completion over its area, require monocular viewing while, in congruous homonymous hemianopia, the visual deficit is present with either eye and, therefore, in binocular viewing. The cortical representations of the part of the visual field corresponding to the blind spot of the contralateral eye is thus serviced by afferent neurons projecting from the homologous area in the ipsilateral eye. Consequently, the cortical area corresponding to the blind spot of the contralateral eye is not a 'hole' but contains monocularly driven cells from the ipsilateral eye and, in monocular viewing, even if these cells are not activated by information coming from the sense organ, they are nonetheless functional. The pattern of intrinsic connectivity in the visual cortex is characterized by the existence of horizontal connections linking different cortical receptive fields with similar response properties (Gilbert, 1985). These connections extend up to 4 mm laterally, which, by virtue of the magnification factor (Virsu and Rovamo, 1979), corresponds to 6° of visual angle at the retinal eccentricity of the blind spot. The actual completion over the blind spot may then result from excitatory or facilitatory influences of surrounding cortical receptive fields on the functionally active neurons representing this part of the visual field. Evidence of excitatory peripheral influence beyond the standard receptive fields in cortically intact animals is now well documented (Doty and Grimm, 1962; Hammond and MacKay, 1981; Gilbert, 1985), and it may be through such a process that the immediate surround of the blind spot determines its filling in. Although speculative, this explanation of completion over the blind spot would predict that electrophysiological recording in monocularly viewing animals stimulated over the retinal area comprising the blind spot should show activation of cortical cells representing the area corresponding to the blind spot of the stimulated eye.

Whether or not this process underlies completion over the blind spot of normal subjects, there are fundamental differences between the cortical representation of the blind spot and that of the hemianopic visual field, the latter being deprived of functional cortical neurons activated by either eye. While analogies can be drawn between the two conditions at a phenomenological level, there are qualitive differences in physiology and anatomy that may preclude a common explanation of perceptual completion over their respective extent.

The failure to demonstrate completion in its simplest form in hemianopic patients suggests that the hemianopic defect does not function as an extended blind spot, and that the occurrence of perceptual completion in these two blind areas may not involve the same underlying mechanisms. As already noted, the retinotopically organized cortical area corresponding to the blind spot of one eye is serviced by functional neurons representing this area of the visual field and originating from the other eye. These functional neurons may thus be activated in phase with the firing of horizontally connected neurons with the same response properties in the vicinity of the blind spot, giving rise to an excitation in the absence of direct stimulation of the senses, and leading to actual signals being transmitted for conscious perception. Such a mechanism may be similar to that underlying the generation of illusory contours in figures such as Kanizsa's (1974) triangle, and evidence has recently been presented of cortical neurons being activated when an illusory contour passes over their receptive field (von der Heydt *et al.*, 1984; Redies *et al.*, 1986). In contrast, genuine perceptual completion in the hemianopic field is an uncommon phenomenon and, when it occurs, requires the involvement of subcortical visual structures whose activation may be enhanced through interaction across the midline. It is a matter for further investigation to determine whether neural connections similar to those postulated to underlie perception in the blind spot exist at a subcortical level and are sufficiently extended to span a large area of the visual field, and to explain why genuine perceptual completion occurs only in a small proportion of hemianopic patients.

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# DEPRESSIVE DISORDERS FOLLOWING POSTERIOR CIRCULATION AS COMPARED WITH MIDDLE CEREBRAL ARTERY INFARCTS

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## SUMMARY

Patients with cerebrovascular lesions in the posterior circulation territory (PC) were compared with patients having middle cerebral artery territory (MCA) strokes for the presence of mood disorders. Both groups showed a similar profile of clinical symptoms of depression during the acute evaluation in hospital. Patients with posterior circulation lesions involving the brainstem and/or cerebellum demonstrated a significantly lower frequency of depression than patients with MCA lesions or patients with posterior circulation lesions involving the left cerebral hemisphere. Moreover, depression following brainstem and/or cellebellar infarcts was of significantly shorter duration than depression following MCA lesions These differences in the frequency and duration of depression following brainstem/cerebellar as compared with MCA lesions were not explained by differences in lesion volume, physical impairment, cognitive deficits or quality of social support. They suggest that PC and MCA induced depression may have different aetiologies.

## INTRODUCTION

For many years, depression has been recognized as a common sequel of strokes (Kraepelin, 1921). In cross-sectional as well as longitudinal studies, we have demonstrated the high prevalence of depression in both acute and chronic stroke populations (Robinson and Price, 1982; Robinson *et al.*, 1983*a*, 1984*a*, 1987). During the acute poststroke period, approximately one-third of patients are significantly depressed and this proportion of depressed patients remains relatively unchanged at 6 months, 1 and 2 yrs follow-up (Robinson *et al.*, 1983*a*, 1984*b*, 1987).

Since more than 80% of strokes occur in the territory of the middle cerebral

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artery (MCA) (Mohr, 1986), these frequencies for depressive disorders mainly reflect mood changes after lesions in this vascular territory. Mood changes following ischaemic lesions in the vertebrobasilar-posterior cerebral artery territory (PC) have never been examined systematically.

The present study examines the frequency, type and longitudinal course of mood disorders in patients with strokes of the posterior circulation territory and compares them with findings in patients with middle cerebral artery territory infarcts.

## METHODS

### *Patients*

Patients included in this study were selected from 154 consecutive admissions to the University of Maryland Hospital for treatment of acute thromboembolic infarction. Fifty-three patients were excluded because of decreased consciousness (stupor or coma) or severe comprehension deficits (patients who did not score within 10 points on test-retest administration of the Zung Depression Scale (Zung, 1965) were excluded). Seven patients were discharged before they could be studied, and 15 patients who could not be classified in either the MCA or PCA lesion groups (they had non-localizing focal signs and negative CT scans) were excluded from further study. For the present investigation, 79 consecutive patients were divided into two groups.

*Posterior circulation (PC) group.* This group consisted of 37 consecutive patients with clinical findings compatible with strokes in the posterior circulation territory (limb and gait ataxia, oculomotor disturbances, nystagmus, Horner's syndrome, hoarseness, dysphagia, facial palsy, internuclear ophthalmoplegia, facial pain, visual field deficits) and/or CT scans showing lesions in the brainstem, cerebellum or hemisphere regions irrigated by the posterior cerebral arteries (according to Damasio, 1983).

*Middle cerebral artery (MCA) group.* This group consisted of 42 consecutive patients with strokes in the territory of the middle cerebral artery (MCA) as demonstrated by clinical and/or CT scan findings (according to Damasio, 1983).

### *Neurological and psychiatric examination*

The neurological examination and diagnosis for all patients at the time of admission to hospital for acute stroke and at follow-up were performed using the criteria established by the Stroke Data Bank of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) (Kunitz *et al.*, 1984). All neurological evaluations and CT scan readings were done blind to the findings on psychopathological examination. Lesion volume (expressed as a percentage of total brain volume) was calculated from the ratio of the largest cross-sectional area of the lesion divided by the cross-sectional area of the whole brain on the slice passing through the largest cross-sectional area of the lateral ventricles.

After giving informed consent, patients were administered a series of standardized quantitative measures of mood, cognitive function, and physical impairment. We have previously shown (Robinson and Benson, 1981; Robinson and Szetela, 1981; Robinson *et al.*, 1983*b*) that these instruments give reliable and valid measurement in this stroke population. Examinations were administered in a private room between 11 am and 2 pm to minimize any possible effect of diurnal mood variation. Longitudinal assessment was carried out by performing repeat evaluations in the hospital following the acute stroke, and in the outpatient clinic at 6 months and at 12 or 24 months poststroke.

The Hamilton Rating Scale for Depression (Hamilton, 1960), a 17-item questionnaire (scores range from 0 to 52) measuring psychological and physiological symptoms of depression, was completed by the interviewer. The Zung Self-Rating Depression Scale (Zung, 1965), which contains 20 questions, (scores range from 25 to 100) was read to each patient and their responses were scored using the four

Zung categories. The Modified Present State Examination (PSE) (Wing *et al.*, 1974), a semistructured psychiatric interview that elicits symptoms related to depression and anxiety, as described in a previous publication (Robinson *et al.*, 1983*a*), was scored by the examiner (possible scores may range from 0 to 144). For each of the depression scales higher scores indicate greater severity of depression.

The MiniMental State Exam (MMSE) (Folstein *et al.*, 1975) and the Johns Hopkins Functioning Inventory (JHFI) (Robinson and Szetela, 1981) were also administered to each patient. The MMSE is an 11-item examination that has been found to be reliable and valid in assessing a limited range of cognitive functions in stroke patients (Robinson *et al.*, 1986). Scores range from 0 to 30 and a score of 23 or below indicates significant cognitive impairment. The JHFI contains 10 items and evaluates the degree of independence of activities of daily living. Scores range from 0 to 27, and higher scores indicate greater degrees of impairment. In conjunction with the psychiatric evaluation, quantitative assessments of social functioning were made using the Social Functioning Exam (SFE) (scores may range from 0 to 1000 with higher scores indicating greater social impairment) (Starr *et al.*, 1983).

Using the symptoms elicited by the PSE, a depression diagnosis was made using DSM-III (American Psychiatric Association, 1980) symptom criteria for either major depression or dysthymic (minor) depression. Although these poststroke mood disorders do not always meet the exact criteria for time and exclusion of organic factors for DSM-III diagnosis, we have shown that the use of symptom clusters of major and minor depression makes an important distinction between these two types of depression. Major and minor depression have a differential association with lesion location (Robinson *et al.*, 1984*a*), response to dexamethasone suppression test (Lispey *et al.*, 1985), 'pseudodementia' (Robinson *et al.*, 1986), clinical severity (Robinson *et al.*, 1983*b*) and longitudinal course (Robinson *et al.*, 1987). The method for conversion from PSE symptoms to DSM-III criteria is available upon request.

### *Statistical analysis*

Statistical analysis was performed using means and SDs, analysis of variance, Student's t test, Mann-Whitney U test and Pearson's correlation coefficient. Frequency distributions were analysed using $\chi^2$ tests with Yates' modification for expected cell sizes below 5.

## RESULTS

### *Background characteristics*

Demographic data are presented in Table 1. The study populations consisted mainly of males in their late 50s and early 60s. There was a slight preponderance of blacks, and the population was primarily from lower socioeconomic classes (i.e., Hollingshead classes IV and V). Four patients in the PC group had a history of psychiatric disorders (3 had a previous history of alcoholism and 1 had previous episodes of anxiety treated with benzodiazepines). Five patients with MCA lesions had a history of psychiatric disorders (2 had a previous history of alcoholism, 1 had previous episodes of anxiety, 1 had previous episodes of depression treated with tricyclic drugs and 1 had an unclear past psychiatric history). There were no significant differences in demographic variables between MCA and PC groups. All patients were evaluated during the first 30 days poststroke, except for 2 patients in the PC group who were assessed during the second month poststroke.

TABLE 1 DEMOGRAPHIC DATA

| | *PC group* | *MCA group* |
|---|---|---|
| No. patients | 37 | 42 |
| Age (yrs) | 60.4 (13.5) | 59.7 (12.1) |
| Sex (% female) | 30 | 42 |
| Race (% blacks) | 62 | 64 |
| Socioeconomic status (% Hollingshead class IV or V) | 65 | 69 |
| Marital status (% married) | 51 | 50 |
| No. of children (mean) | 2 | 3 |
| No. of siblings (mean) | 4 | 5 |
| Origin (% urban) | 43 | 43 |
| Education (mean yrs) | 8.8 (4.4) | 9.8 (3.7) |
| Tobacco (% smoking more than 1 pack per day) | 19 | 38 |
| Alcoholism (% hospitalized because of alcoholism) | 8 | 5 |
| Familial history of psychiatric disorders (% positive) | 11 | 5 |
| Personal history of psychiatric disorders (% positive) | 11 | 12 |
| Previous medical illness (% with life-threatening illness) | 18 | 14 |

SDs are shown in brackets

### *Neurological findings*

On neurological examination (Table 2), half of the PC patients showed a motor deficit, which was predominantly mild. More than a third showed sensory as well as visual field deficits. All patients with PC hemisphere lesions had a positive CT scan. Twenty-three patients (62%) had brainstem and/or cerebellar signs. Based on clinical signs and/or CT scan imaging, 39% of the patients with cerebellar/brainstem signs had cerebellar involvement, while 30% had midbrain lesions, 26% had lesions in the basis pontis, 22% had paramedian infarcts of the tegmentum pontis and 9% had lateral medullary infarctions.

The MCA group (Table 2) had a high frequency of motor deficits, followed by sensory deficits. One-third of the patients with a left-sided MCA lesion also had aphasia. Based on clinical signs and/or CT scan imaging, 55% had left hemisphere lesions and 45% had right hemisphere lesions. While 62% had restricted subcortical damage (mainly involving the basal ganglia and anterior limb of the internal capsule), 33% had cortical involvement with minor subcortical extension (mainly involving the rolandic operculum) and 5% had large corticosubcortical infarctions (involving the whole MCA territory).

Although 5 patients had clinical symtoms that could overlap with symptoms due to lesions in the PC territory, all of them had positive CT scans with lesions in the MCA territory.

### *Psychopathological findings*

Based on the information elicited by the PSE, symptoms found in patients with diagnosed depression were divided into affective and autonomic symptoms of depression. There was no difference in frequency of affective or autonomic symptoms of depression between MCA and PC patients with major or minor depression (Table 3).

TABLE 2 NEUROLOGICAL EXAMINATION (% OF PATIENTS)

| | *PC group* | *MCA group* |
|---|---|---|
| No of patients | 37 | 42 |
| Paresis | 57 (21) | 81 (34) |
| Mild | 32 (12) | 50 (21) |
| Moderate | 19 (7) | 21 (9) |
| Severe | 5 (2) | 10 (4) |
| Sensory deficits | 35 (13) | 38 (16) |
| Visual field deficits | 38 (14) | 14 (6) |
| Cranial nerve involvement | 41 (15) | 0 |
| Cerebellar signs | 24 (9) | 0 |
| Aphasia | 3 (1) | 21 (9) |
| Broca | 0 | 10 (4) |
| Wernicke | 0 | 5 (2) |
| Anomia | 3 (1) | 7 (3) |
| Lesions on CT scan | 49 (18) | 71 (30) |

No of patients are shown in brackets

TABLE 3 SYMPTOMS IN PATIENTS WITH MAJOR DEPRESSION (% OF PATIENTS)

| | *MCA group* | *PC group* |
|---|---|---|
| No. of patients | 14 | 12 |
| Affective symtoms | | |
| Worrying | 79 (11) | 75 (9) |
| Brooding | 50 (14) | 50 (6) |
| Loss of interest | 43 (6) | 67 (8) |
| Hopelessness | 64 (9) | 50 (6) |
| Suicidal ideation | 21 (3) | 17 (2) |
| Social withdrawal | 43 (6) | 8 (1) |
| Self-deprecation | 36 (5) | 33 (4) |
| Ideas of reference | 50 (7) | 42 (5) |
| Autonomic symptoms | | |
| Morning depression | 64 (9) | 67 (8) |
| Loss of weight | 79 (11) | 75 (9) |
| Initial insomnia | 64 (9) | 33 (4) |
| Final insomnia | 50 (7) | 42 (5) |
| Anergia and retardation | 43 (6) | 25 (3) |
| Loss of libido | 64 (9) | 50 (6) |

No of patients are shown in brackets

### *Inpatient psychiatric diagnosis*

Based on structured psychiatric interview using the PSE, 10 patients (27%) from the PC group were found to be depressed immediately after the acute event (4 had major and 6 had minor depression). Among the 37 patients with PC infarcts, 26 patients (70%) were seen at 6 months follow-up, and 24 patients (65%) were seen between 1 and 2 yrs poststroke. Six patients (16%) had only 1 evaluation which was performed immediately after the acute event (3 patients died before the 6 months follow-up and 3 were lost to follow-up). At the time of their initial admission, there were no statistically significant differences between the follow-up

TABLE 4 DEMOGRAPHIC AND PSYCHIATRIC DIAGNOSIS FOR PC PATIENTS WITH AND WITHOUT 1–2 YRS FOLLOW-UP

| | *Follow up* | *Non-follow-up* |
|---|---|---|
| No of patients | 31 | 6 |
| Age (yrs) | 60.8 (13 2) | 60.8 (11) |
| Sex (% females) | 35 | 17 |
| Race (% black) | 63 | 50 |
| Socioeconomic status (% Hollingshead class IV–V) | 68 | 67 |
| % of patients with major depression | 13 | 17 |
| % of patients with minor depression | 16 | 17 |
| Present State Exam (mean) | 8 4 (6.9) | 5.3 (3 8) |
| Zung Depression Scale (mean) | 37.6 (8.2) | 39 (10.4) |
| Hamilton Depression Scale (mean) | 6 3 (5 8) | 7 2 (6 2) |
| Social Functioning Exam (mean) | 223 (130) | 260 (185) |

SDs are shown in brackets

and non-follow-up groups in demographic variables, depression, social functioning, cognitive or physical impairment scores (Table 4).

Among the patients with MCA infarcts, 20 patients (48%) developed depression immediately after the acute event (11 had major depression and 9 had minor depression). Twenty-six patients (62%) had a follow-up evaulation at 6 months, and the whole group of 42 patients were evaluated between 1 and 2 yrs poststroke.

Although the MCA group contained a greater percentage of depressed patients than the PC group, the difference fell short of statistical significance ($\chi^2 = 3.54$, df = 1, $P = 0.054$).

### *Relationship between depression, lesion location, and longitudinal course*

The PC group was divided based on lesion location. There were 23 patients with restricted cerebellar and/or brainstem involvement, 6 patients with left hemisphere lesions and 8 patients with right hemisphere lesions. During the follow-up period, the groups with cerebellar/brainstem damage showed a progressive decrease in the frequency of depression. Immediately after the acute event, 8 of 23 patients (35%) were depressed. Four patients (with lesions in the paramedian tegmentum pontis and cerebellum, midbrain and basis pontis, cerebellum, and lateral medulla) showed major depression, while 4 patients (with lesions in the paramedian tegmentum pontis, midbrain and basis pontis, cerebellum, and basis pontis) showed minor depression. Seventeen patients (74%) were seen at 6 months follow-up, and 11 patients (48%) were seen between 1 and 2 yrs follow-up. At 6 months follow-up 4 of 17 patients (24%) were depressed (2 patients with major depression had lesions in the midbrain and basis pontis, while 2 patients with minor depression had lesions in the paramedian tegmentum pontis). At 1–2 yrs follow-up only 1 of 11 patients (9%) was depressed (major depression after a cerebellar lesion).

All 6 patients with PC left hemisphere lesions were examined at 6 months and between 1 and 2 yrs follow-up. This group showed a marked increase in the frequency of depression during the follow-up period; 2 of 6 (33%) at the initial evaluation, 6 of 6 (100%) at 6 months follow-up and 4 of 6 (67%) at 1–2 yrs follow-up.

Eight patients with PC right hemisphere lesions had in-hospital evaluations; 3 were seen at 6 months follow-up and 3 between 1 and 2 yrs follow-up. None of these patients showed depressive symptoms (0% depression during the acute event and at both 6 months and 1–2 yrs follow-up). One patient (13%) with a right hemisphere lesion was unduly cheerful during the acute event, another at 6 months and a third at 1–2 yrs follow-up. At both 6 months and 1–2 yrs follow-up, the group with left hemisphere lesions showed a significantly higher frequency of depression as compared with the brainstem and right hemisphere groups (6 months follow-up $\chi^2=13.1$, df=2, $P=0.002$; 1–2 yrs follow-up $\chi^2=8.0$, df=2, $P=0.017$).

The MCA group was also divided based on lesion location. There were 23 patients with left hemisphere lesions and 19 patients with right hemisphere lesions. During the follow-up period, the group with left hemisphere lesions showed a relatively constant frequency of depression (11 patients (48%) in the acute stage, 9 patients (56%) at 6 months and 11 patients (48%) at 1–2 yrs follow-up). A similar frequency was observed for the group with right hemisphere damage (9 patients (47%) in the acute stage, 5 patients (50%) at 6 months and 8 patients (42%) at 1–2 yrs follow-up). Major depression, however, was significantly associated with left hemisphere lesions (11 out of 14 (78%) MCA patients who developed major depression had left hemisphere lesions ($\chi^2=4.80$, df=1, $P<0.03$), while there was a trend for minor depressions to be more frequent in the group with right hemisphere lesions (8 out of 12 patients (67%) with minor depression had right-sided strokes ($\chi^2=3.11$, df=1, $P=0.077$).

Since the PC patients with hemisphere involvement showed the same frequency over time and lateralized response to stroke that we have shown for anterior cortical and subcortical lesions (Starkstein *et al.*, 1987), we compared the group with restricted cerebellar/brainstem involvement to the MCA group. In-hospital frequencies of depression (major plus minor) were 48% for the MCA group and 35% for the brainstem/cerebellar group. At 6 months follow-up, however, frequencies of depression were 54% and 24%, respectively ($\chi^2=3.89$, df=1, $P<0.05$), and at 1–2 yrs follow-up frequencies of depression were 45% and 9%, respectively ($\chi^2$ Yates $=3.6$, df=1, $P=0.05$).

This rapid decline in the frequency of depression over time demonstrated in the brainstem/cerebellar lesion group (compared with the MCA group) was also confirmed by looking at individual patients. While 82% of MCA patients with in-hospital depression were still depressed at 6 months follow-up, only 20% of the cerebellar/brainstem patients were depressed at this time-point ($\chi^2$ Yates= 3.7, df=1, $P=0.05$). At 1–2 yrs follow-up, 68% of the MCA patients with in-hospital depression were still depressed, while none of the cerebellar/brainstem patients with in-hospital depression were depressed at this time-point ($\chi^2$ Yates=4.08, df=1, $P<0.05$). In addition, mean PSE scores from in-hospital to 1–2 yrs follow-up were significantly lower for the brainstem/cerebellar group than the MCA patients with in-hospital depression over the same time period (repeated measures ANOVA from in-hospital to 1–2 years: Interaction (group vs trial) $F = 6.14$, $df = 1, 23$, $P < 0.05$. Mean values for in-hospital PSE scores for MCA and cerebellar/brainstem depressed patients were 17.6 and 17.8, respectively ($t = -0.47$, $P =$ n.s.) whereas PSE scores for MCA and PC patients at 1–2 yrs follow-up were 16.0 and 6.5, respectively ($t = -3.22$, $P < 0.001$). This difference also remained significant after the data were analysed using a nonparametric test (Mann-Whitney $U(6, 19) = 92.5$, $P < 0.05$).

This significantly shorter course of depression in the brainstem, as compared with the MCA group, could not be explained by the PC group having smaller lesion volumes since there was no significant correlation between lesion volume and depression scores either in the hospital or at 1–2 yrs follow-up (correlation coefficients between lesion volume and PSE, Hamilton and Zung depression scores ranged from 0.05 to 0.30).

### *Relationship between depression and physical impairment, cognitive impairment and social functioning*

The PC group was segregated in three subgroups based on psychiatric diagnosis (major, minor or no depression) for the in-hospital diagnosis. Depression scores were, as expected, significantly different between the three groups, but differences were not significant in scores of cognitive impairment, activities of daily living, or social supports (Table 5).

TABLE 5 SCORES OF DEPRESSION, COGNITIVE IMPAIRMENT, ACTIVITIES OF DAILY LIVING AND SOCIAL FUNCTIONING

| *PC group* | *Major depression* | *Minor depression* | *No depression* |
|---|---|---|---|
| No. of patients | 4 | 6 | 27 |
| Present State Exam* | 18.2 (5.1) | 14.6 (5.5) | 4.5 (3.3) |
| Hamilton Depression Scale* | 15.8 (6.5) | 8.5 (5.8) | 4.6 (4.1) |
| Zung Depression Scale* | 51.4 (11.1) | 41.3 (8.7) | 35.5 (6.0) |
| MiniMental State | 26 (4.5) | 22.6 (7.8) | 22.2 (5.4) |
| Johns Hopkins Inventory | 3.0 (2.5) | 5.6 (8.5) | 5.8 (4.7) |
| Social Functioning Exam | 299 (235) | 243 (108) | 224 (144) |
| MCA group | | | |
| No. of patients | 11 | 9 | 22 |
| Present State Exam* | 22.0 (7.3) | 12.8 (4.2) | 4.5 (3.1) |
| Hamilton Depression Scale* | 15.5 (6.4) | 8.2 (2.7) | 3.7 (2.5) |
| Zung Depression Scale* | 59.0 (14.4) | 45.1 (10.3) | 35.0 (6.0) |
| MiniMental State | 20.0 (6.8) | 23.3 (5.0) | 23.0 (5.8) |
| Johns Hopkins Inventory** | 12.7 (5.9) | 6.8 (6.4) | 5.9 (5.2) |
| Social Functioning Exam | 168 (128) | 206 (77) | 179 (129) |

*$P < 0.001$, **$P < 0.05$. SDs are shown in brackets.

Correlations between depression scores and scores of cognitive status, physical impairment and social functioning were calculated for the evaluation carried out at the acute event. No statistically significant correlations were found between depression and either physical, cognitive or social impairments (correlation values ranged from 0.05 to 0.16).

When the PC group was divided into those with hemisphere lesions and those with brainstem/cerebellar lesions, there were no significant correlations between depression scores and either JHFI score, MMSE score or SFE scores for any lesion location (correlation values ranged from 0.12 to 0.22 for the cerebellar/brainstem group (df = 21), and from 0.03 to 0.42 for the PC hemisphere group (df = 12)).

For the MCA group, depression scores were significantly different between major, minor and nondepressed patients. Patients with major depression had significantly higher scores in activities of daily living (JHFI) than patients with minor or no depression (Table 5).

Correlations between depression scores and scores of cognitive status, physical impairment and social functioning were calculated for the in-hospital evaluation. The only statistically significant correlations were between physical impairment (JHFI) scores and depression scores (PSE vs JHFI $r = 0.40$, df = 40, $P < 0.01$, Hamilton vs JHFI $r = 0.38$, df = 40, $P < 0.05$, Zung vs JHFI $r = 0.30$, df = 40, $P < 0.05$).

## DISCUSSION

This study has examined the frequency, severity, phenomenology and longitudinal course of depression produced by strokes in the posterior circulation territory (PC), and compared them with depression produced by cerebrovascular lesions in the territory of the middle cerebral artery (MCA). Although the initial clinical presentation and the frequency of depression were similar for patients with PC and MCA lesions, patients with brainstem/cerebellar infarcts had a significantly lower frequency of depression at 6 months or more after stroke and a significantly shorter duration of depression than patients with MCA lesions.

The fact that cross-sectional (i.e., in-hospital) symptom analysis did not demonstrate significant differences between MCA and brainstem/cerebellar major depressions is not surprising since clinical presentations are frequently similar even when the underlying aetiologies are quite different (e.g., congestive heart failure produced by cardiomyopathy or myocardial infarction may have similar clinical presentations). Autonomic and affective symptoms of depression in MCA and PC patients were also found to have the same frequency as those reported for melancholic and nonmelancholic endogenous depression (Davidson and Turnbull, 1986). This finding is also consistent with our previous report (Lipsey *et al.*, 1986) that patients with poststroke major depression and patients with 'endogenous' (i.e. non-brain-injured) major depression have very similar symptom profiles.

Before further discussion, one limitation of this study should be pointed out. Although 84% of patients with PC strokes were evaluated at least twice after the acute event, 16% of the patients had no follow-up examinations. This being the case, our present findings on the frequency and course of depression after posterior circulation strokes may have been influenced by this lack of complete follow-up. Our findings, therefore, are tentative and should be interpreted with this in mind. There were, however, no differences between patients with and without follow-ups in demographic variables, in-hospital depression scores, scores of cognitive and physical impairment, or scores of social functioning.

To our knowledge this is the first time a systematic study of mood changes after stroke lesions in the PC territory has been undertaken. Miller Fisher (1986) recently stated that in his experience, depression is a prominent finding in patients with lesions in the posterior circulation territory, especially when the left hemisphere is involved. Trimble and Cummings (1981) have also described 2 patients who developed severe depression following brainstem lesions. The present study empirically corroborates these reports, as it demonstrates that more than a third of patients with lesions in the posterior circulation territory develop depression (this frequency may be even higher when the lesion affects the left cerebral hemisphere).

Our finding that the longitudinal course of MCA depressions appears to be different than the course of cerebellar/brainstem depressions raises the question whether the same mechanism is responsible for both MCA and cerebellar/brainstem induced depression. We have suggested, based on our laboratory work (Robinson, 1979), that damage to the ascending biogenic amine pathways may be important in the production of depression associated with MCA infarcts (Robinson *et al.*, 1984). These pathways arise in the brainstem and project anteriorly through the median forebrain bundle, disperse into the caudate, and pass into the frontal cortex (Morrison *et al.*, 1979). We suggested that the association of depression with left frontal cortical or subcortical lesions (Starkstein *et al.*, 1987) may be explained by more anterior lesions (more upstream and closer to the cell bodies of origin) producing greater depletions of catecholamines than more posterior lesions (more downstream). The biogenic amine pathways also have an asymmetric distribution (Oke *et al.*, 1978; Glick *et al.*, 1982), and we have demonstrated in an animal model of stroke that right and left cortical as well as subcortical lesions produce a lateralized behavioural response (Robinson, 1979; Kubos *et al.*, 1987). We have also shown that this lateralized behaviour correlates with asymmetric catecholamine depletion (Robinson, 1979). Based on these data we have suggested that biochemical asymmetries may underlie the production of depression after left hemisphere cortical and subcortical lesions and undue cheerfulness/indifference after right hemisphere cortical or subcortical lesions (Starkstein *et al.*, 1987). Hemisphere PC lesions produced a similar frequency, duration of depression, clinical symptoms, and lesion lateralization as MCA lesions. These findings suggests that the pathogenesis of poststroke depression might be similar for both MCA and PC lesions when there is hemisphere involvement. Patients with cerebellar/brainstem lesions, however, showed a significantly lower frequency of depression as well as shorter duration of depression than both the MCA and left PC groups. The vertebrobasilar system perfuses the noradrenergic, serotoninergic and dopaminergic cell bodies, as well as their most proximal projections. If biogenic amine depletions are important in the production of mood disorders induced by hemisphere infarcts, lesions affecting the cell bodies or proximal projections might also be associated with a high frequency of depression.

Although there was no specific pattern of lesion location and depression (depression was similarly associated with lesions in the pons, midbrain and cerebellum) several hypotheses might be proposed to explain our present findings. For instance, cerebellar/brainstem lesions, because of their relatively small size, might produce less biogenic amine depletion than MCA lesions (although we found no correlation between lesion volume and depression). In addition, by leaving postsynaptic cortical or subcortical structures unharmed, brainstem lesions might allow compensatory mechanisms such as receptor supersensitivity to develop more rapidly than following MCA lesions. Alternatively, 'remote effects' of cerebellar/brainstem lesions might also be associated with the production of poststroke depression. Supratentorial (mainly frontocortical) lesions have also been shown to produce contralateral cerebellar hypometabolism (Pantano *et al.*, 1986) and disruption of direct corticocerebellar pathways has been implicated in this phenomenon. If a cerebellar lesion may also induce frontocortical hypometabolism, this frontocortical dysfunction could lead to depression by the same mechanism as cortical lesions. The relatively short duration of depression after cerebellar lesions could then be attributed to the relatively brief duration of the hypometabolic phenomena (Pappata *et al.*, 1987). Finally it might be hypothesized that damage to descending, rather than ascending, biogenic amine pathways was associated with depression following cerebellar/brainstem lesions. Descending spinal projections from the locus coeruleus have different cell bodies of origin than the ascending cortical projections (Westlund and Coulter, 1980). Thus these descending neurons may not connect to the limbic system in the same way as the ascending neurons and this might lead to lower frequency or duration of depression.

Although further research will be required to determine the aetiology of poststroke depression, and other factors, such as previous personality, severity of physical impairment or social support may contribute to such depression, our finding that the course of MCA and cerebellar/brainstem associated depression is different may begin to separate out various aetiological types of depression after brain injury. Thus far, the only subclassification of depression which has been suggested to be of importance in brain-injured patients is major versus minor poststroke depression (Robinson *et al.*, 1987). With the identification of depression induced by brainstem/cerebellar versus hemisphere infarcts, we may be demonstrating another important subclassification of poststroke depression which has implications for prognosis, aetiology and response to treatment.

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# PROJECTION TO THE CEREBRAL CORTEX FROM PROXIMAL AND DISTAL MUSCLES IN THE HUMAN UPPER LIMB

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## SUMMARY

Motor-point stimulation using insulated microelectrodes has been used to assess the cerebral projection from a number of single muscles in the human upper limb Previous studies with intrafascicular neural stimulation have revealed a short-latency cortical projection from group I muscle afferents of intrinsic muscles of the hand but this technique is unsuitable to study the projection of afferents from proximal muscles. In 6 subjects, stimuli were delivered to the motor point of the following muscles: anterior deltoid, biceps brachii (short head), flexor carpi radialis, extensor digitorum communis, abductor pollicis brevis and first dorsal interosseous. The mean latency of the early cortical negativity was 15.0 ms for deltoid, 16.4 ms for biceps, 18.8 ms for flexor carpi radialis, 18.8 ms for extensor digitorum communis, 21.9 ms for abductor pollicis brevis and 25.0 ms for first dorsal interosseous. The amplitude of cerebral potentials from individual muscles was smaller than that produced by stimulation of the digital nerves of the index or little finger and did not vary systematically between proximal and distal muscles. This study provides direct evidence for a short-latency cortical projection from proximal muscles of the upper limb. The results are consistent with psychophysical studies which have proposed a role for intramuscular receptors in kinaesthesia at both proximal and distal joints.

## INTRODUCTION

Although there is a considerable literature on kinaesthesia and on long-loop (possibly transcortical) reflexes involving arm and forearm muscles, there is no definitive evidence that afferents from muscles of the shoulder, arm or forearm project to cerebral cortex in human subjects. However, there is evidence for a short-latency projection of large diameter muscle afferents to the sensorimotor cortex in animals (e.g. Oscarsson *et al.*, 1966; Phillips *et al.*, 1971; Lucier *et al.*, 1975; Heath *et al.*, 1976; Lemon, 1979; for review, *see* Wiesendanger and Miles, 1982) and in man (Starr *et al.*, 1981; Burke *et al.*, 1981; Gandevia *et al.*, 1984; Gandevia, 1985; for review, *see* Burke and Gandevia, 1986). Afferents from Golgi tendon organs as

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well as muscle spindle endings may contribute to this projection, at least in the cat (McIntyre *et al.*, 1984).

Some evidence for a cortical projection of muscle afferents has been obtained both for the human upper limb (Gandevia *et al.*, 1984; Abbruzzese *et al.*, 1985; Crammond *et al.*, 1985) and lower limb (Burke *et al.*, 1981; Starr *et al.*, 1981; Burke *et al.*, 1982; Gandevia *et al.*, 1982; Cohen *et al.*, 1985). However, much of this evidence for a cortical projection of human group I muscle afferents is indirect, based upon cerebral potentials produced by percussion over tendons and by joint movement (Starr *et al.*, 1981; Abbruzzese *et al.*, 1985; Cohen *et al.*, 1985; *see also* Crammond *et al.*, 1985). Neither tendon percussion nor joint movement is a selective stimulus for intramuscular receptors. Much less is known about the somatotopic projection of muscle afferents to the cortex compared with the cutaneous afferent projection (for review, *see* Kaas, 1983).

More definitive evidence has come from selective stimulation of muscle afferents using electrical stimuli delivered through a microelectrode in a purely motor fascicle of limb nerves, but these studies have been performed on only a limited number of fascicles innervating the most distal limb muscles (Burke *et al.*, 1981, 1982; Gandevia *et al.*, 1984; Gandevia, 1985). In the present study, the technique of motor-point stimulation using an intramuscular microelectrode has been adapted to allow comparison of the cortical projection of afferents from proximal and distal muscles in the upper limb. The results confirm the previous finding of a short-latency cortical projection for group I muscle afferents from intrinsic muscles of the hand (Gandevia *et al.*, 1984; Gandevia, 1985) and demonstrate, for the first time, such a projection for group I afferents from a number of individual muscles throughout the upper limb. A preliminary account of some findings has been presented (Gandevia and Burke, 1986).

## METHODS

The major series of experiments in this study has involved repeated experiments on 6 subjects, ranging in age from 31 to 59 yrs, each of whom has been studied on 3 to 8 occasions. An additional 5 subjects, unfamiliar with the techniques or purpose of the study, have been investigated in a single experimental session to check on the generality of findings noted in the major series. Informed consent was obtained and the procedures used have the approval of the institutional ethics committees.

### *Stimulation techniques*

Muscle afferents were stimulated using an insulated tungsten microelectrode which was inserted at the motor point of the muscle under study The following muscles were usually studied: abductor pollicis brevis, first dorsal interosseous, flexor carpi radialis, a digital portion of extensor digitorum communis, biceps brachii (short head) and anterior deltoid For each muscle the motor point was located by stimulation through a probe electrode (diameter 2 mm). A microelectrode was inserted at the site at which the threshold for evoked contraction with the probe was lowest and its position adjusted to produce a twitch contraction at a stimulus intensity below 1 mA. Usually these sites approximated to the junction of the proximal third and the distal two-thirds of the muscle belly. The insulation was removed from the stimulating cathode for about 200–300 μm for the intrinsic muscles of the hand and 500–1,000 μm for the larger proximal muscles. The anode was either a similar microelectrode or an uninsulated platinum alloy needle inserted 2–3 cm distal to the cathode. With optimal electrode positions the stimulus required for a muscle twitch was no more than 1 mA. The usual stimulus intensity for studies of cerebral potentials was 1–3 mA. In one study a stimulus intensity of 6 mA was used. Stimuli were rectangular pulses of 0.3–1.0 ms duration delivered from a constant current source at 2 Hz. At the usual intensity the stimuli produced a nonpainful twitch contraction of the muscle. Subjects sometimes noted a dull ache in the region of the muscle and this subsided over several minutes. Insertion of concentric needle electrodes at the motor point during routine electromyography is commonly associated with this sensation. The stimuli did not produce any local cutaneous sensation, radiating cutaneous paraesthesiae, or sharp sensations localized to joints distal to the intramuscular site.

In 9 of the subjects the digital nerves of the index finger were stimulated at three times sensory threshold using ring electrodes over the proximal phalanx. The median nerve was also stimulated 2 cm proximal to the wrist. Stimulus intensity was adjusted to give a strong motor response in thenar muscles and radiating paraesthesiae.

In two studies involving biceps brachii no overt cerebral potential was detected. To establish that the intramuscular stimuli had activated large diameter group I afferents the intramuscular stimuli were delivered during a weak voluntary isometric contraction of the muscle to produce an H reflex in that muscle. For these studies the electromyographic activity (EMG) was recorded with closely spaced (15–25 mm) surface electrodes placed just distal to the intramuscular electrodes (bandpass 10–1,500 Hz), and an anode was placed 2–3 cm lateral to the motor point.

### *Recording and analysis techniques*

Cerebral activity was recorded with subdermal needle electrodes using a montage of 4 electrodes in most studies. The active electrodes were located at the following positions: (1) at the conventional site for a maximal potential to median nerve stimulation at the wrist, i.e., 1 cm posterior and 7 cm lateral to the vertex ('hand area' electrode); (2) 3–5 cm lateral to the vertex ('intermediate' electrode); (3) 3 cm anterior and 5 cm lateral to the vertex ('anterior' electrode); and (4) the vertex ('vertex' electrode). In initial studies of the projection from forearm and hand muscles the latter two electrode sites were not used routinely The reference electrode was located at the earlobe contralateral to the side of nerve stimulation. Activity was amplified, filtered (1 Hz–1.5 kHz) and averaged with a sampling rate of 10 kHz Sequential sets of 256 responses were averaged alternately into two stores of the averager to give duplicates containing a total of 1024–4096 responses for each average. Individual sweeps with large EMG or other artefacts were automatically rejected by the averager. In one session in each of 4 subjects the afferent volley produced by stimulation within an intrinsic muscle of the hand was monitored at both the elbow and axilla using needle electrodes.

The averaged cerebral responses to stimulation at the motor point were examined to determine (1) whether a reproducible potential was recorded, (2) the latency of the first definite negativity (N1) at the most 'active' electrode, and (3) the amplitude of the first definite negativity to the subsequent positivity (N1-P1) for the various electrode sites. Because the components of cerebral potentials from single proximal and distal muscles had different latencies they were not labelled according to the convention of polarity and latency but by the polarity and the number of the component. Thus 'N1' corresponds to N19 with potentials produced by stimulation at the wrist, and 'P1' is the following positive inflection (P23–29). Based on direct recording this initial negativity is believed to reflect the arrival of the thalamocortical volley (e g , Albe-Fessard *et al.*, 1986). In some instances for the deltoid, in which there was uncertainty about the initial negativity, a bipolar montage was reconstructed by subtraction of two potentials recorded with an earlobe reference. If no potential was detected within 50 ms following the stimuli, then it was checked whether weaker stimuli delivered through the same electrodes evoked H reflexes from the muscle under study. The latency and amplitude measurements given in results were derived from measurements of the potentials recorded with an earlobe reference. In each session the projection from up to three muscles was investigated.

## RESULTS

Cerebral potentials were recorded following intramuscular stimulation at the motor point of both proximal and distal muscles. In each subject observations were made for 2 intrinsic hand muscles (abductor pollicis brevis, first dorsal interosseous), 2 muscles from the forearm (flexor carpi radialis, extensor digitorum communis) and 2 large proximal muscles (the short head of biceps brachii, anterior deltoid). Although the potentials for individual muscles were relatively small (Table; figs 1,2; *see also* below) they were detected for more than 90% of intramuscular stimulation sites. The usual stimulus intensity (about 1.5 times motor threshold) produced a brisk muscle twitch but no local cutaneous sensation or radiating cutaneous or joint paraesthesiae. Clear cerebral potentials could also be recorded with stimuli which produced a liminal contraction of the innervated muscle. Given the location of the stimulating electrode, the stimulus intensity required to evoke a potential, and their relatively short latencies (*see* Table) it is likely that the responsible afferents were rapidly conducting and of low electrical threshold. The probability that the cerebral potential evoked by intramuscular stimulation reflects activity in group I muscle afferents is specifically considered in the Discussion. The afferent volley produced by stimulation within intrinsic muscles of the hand was monitored in four studies with 'near nerve' recordings (fig. 3). The volley was recorded at stimulus intensities which evoked a cerebral potential. The conduction velocity of the muscle afferent volley was similar to that for the most rapidly conducting afferents within the digital nerves.

TABLE CEREBRAL POTENTIALS PRODUCED BY MOTOR-POINT STIMULATION
RESULTS EXPRESSED AS MEAN ± SEM

| | *N1 (ms)* | *P1 (ms)* | *Amplitude (μV)* |
|---|---|---|---|
| First dorsal interosseous | 25.0 ± 0.44<br>(23.4 to 26.8) | 28.1 ± 1.1<br>(24.8 to 34.0) | 470 ± 170<br>(100 to 1260) |
| Abductor pollicis brevis | 21.9 ± 0.61<br>(20.6 to 25.0) | 25.5 ± 0.98<br>(23.0 to 29.4) | 430 ± 100<br>(200 to 800) |
| Extensor digitorum communis (III) | 18.8 ± 0.65<br>(16.8 to 21.0) | 22.8 ± 1.1<br>(18.2 to 26.6) | 540 ± 220<br>(120 to 1240) |
| Flexor carpi radialis | 18.8 ± 0.80<br>(17.2 to 20.6) | 21.0 ± 0.90<br>(19.0 to 23.2) | 310 ± 140<br>(100 to 790) |
| Biceps brachii (short head) | 16.4 ± 0.35<br>(15.2 to 17.6) | 19.3 ± 0.57<br>(17.4 to 21.4) | 385 ± 70<br>(200 to 640) |
| Anterior deltoid | 15.0 ± 0.49<br>(13.2 to 16.8) | 17.6 ± 0.58<br>(16.0 to 19.0) | 480 ± 150<br>(140 to 1000) |

The characteristic waveform of the cerebral potentials produced by intramuscular stimulation was usually similar to that produced by stimulation of distal cutaneous or mixed nerves (fig. 1). This similarity was most notable for the cerebral potentials produced by stimulation within intrinsic hand muscles (abductor pollicis brevis,

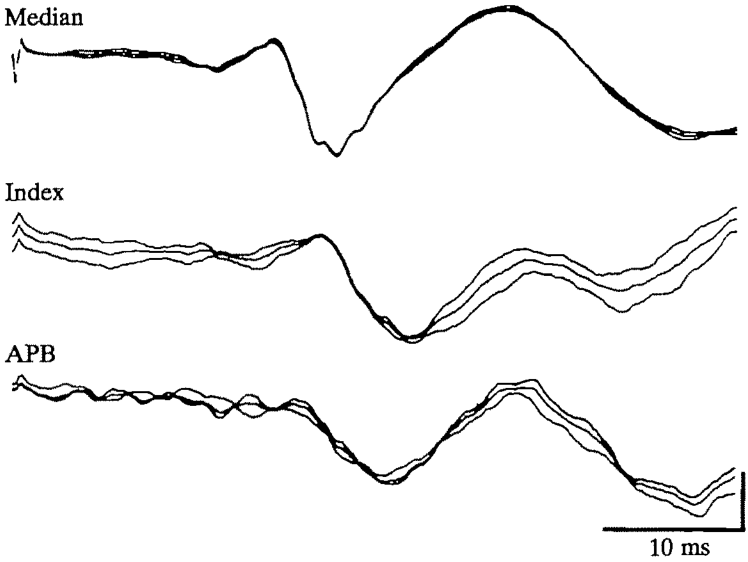

FIG 1. Cerebral potentials produced in 1 subject by stimulation of the median nerve at the wrist (*upper traces*), digital nerves of the index finger at the proximal phalanx (*middle traces*) and the motor point of abductor pollicis brevis (APB) via a microelectrode (*lower traces*). In this and subsequent figures each set of traces contains 2 average responses and the mean of the two averages. The 'active' electrode was over the 'hand area' with the reference on the contralateral earlobe (*see* Methods). Negativity at the former electrode produces an upgoing deflection. Stimuli were delivered at three times the relevant sensory and/or motor threshold. Averages of 512 responses. Vertical calibration (from upper traces downwards). 5 $\mu$V, 2 $\mu$V, 1 5 $\mu$V.

first dorsal interosseous, abductor digiti minimi) and by stimulation of the digital nerves to the second or fifth digits. However, the potentials produced by intramuscular stimulation did not always have a clear initial cortical negativity, though this can usually be defined for digital nerve stimulation even at weak intensities (e.g., Gandevia *et al.*, 1983; *see also* fig. 7).

The amplitude of the cerebral potentials produced by motor-point stimulation was about 0.5 $\mu$V for the initial negative-positive component (N1-P1; Table; *see also* below). This measurement varied widely between subjects and had a coefficient of variation of about 40% for 1 subject studied on 5 occasions, possibly because slight variations in electrode position have greater effects with intramuscular stimulation than with surface stimulation. In contrast, the latencies of the earliest components rarely varied by more than 5% between recording sessions. As noted previously for cerebral potentials produced by stimulation of the median nerve (Giblin, 1964), those produced by motor-point stimulation had a consistent waveform when the same subjects were studied over several years. Although these potentials were comparatively small in amplitude, they were actually larger than expected given the fraction of the parent nerve which was stimulated (*see* Discussion). For example, the N1-P1 amplitude for abductor pollicis brevis was about 50% (mean for individual subjects) of that for the equivalent component for the potential produced by stimulation of the digital nerves of the index finger and about 15% of that for stimulation of the whole median nerve at the wrist.

### *Cerebral projection from different upper limb muscles*

Results from the 6 subjects for the 6 muscles examined in detail are summarized in the Table and illustrated for 1 subject in fig. 2. The average latency of N1 for stimulation within abductor pollicis brevis was 21.9 ms (range 20.6–25.0 ms). It was shorter than the latency to stimulation within the first dorsal interosseous in each subject by an average of 3.1 ms (range 1.8–5.2 ms). This presumably reflects, in part, the longer course within the palm of the ulnar fascicle innervating the first

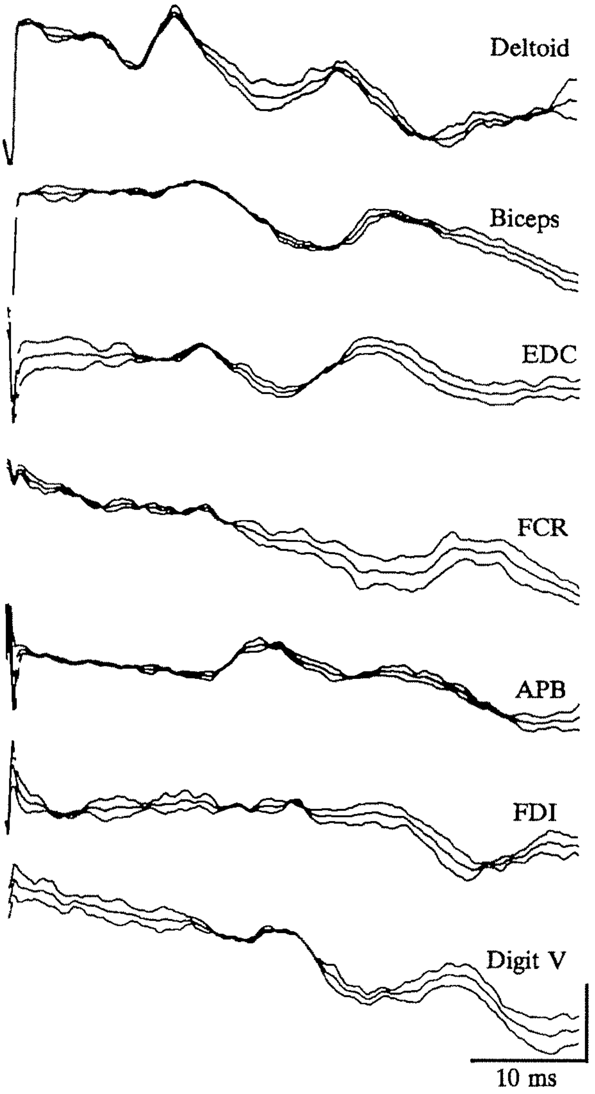

FIG 2 Cerebral potentials produced in 1 subject by stimulation of the motor point of anterior deltoid (*top traces*), short head of biceps brachii, extensor digitorum communis (EDC) (middle finger component), flexor carpi radialis (FCR), abductor pollicis brevis (APB), first dorsal interosseous (FDI) and by stimulation of the digital nerves of the little finger (*bottom traces*) Stimuli were delivered at three times the relevant motor or sensory threshold. All traces obtained with an earlobe reference. The position of the active electrode, number of responses in each average and vertical calibration were as follows· deltoid—lateral electrode (*see* Methods), n = 1024, 1.4 $\mu$V; biceps—anterior electrode, 2048, 1 4 $\mu$V, extensor digitorum communis—anterior electrode, 1024, 1 $\mu$V; flexor carpi radialis—anterior electrode, 3000, 1 $\mu$V, abductor pollicus brevis—anterior electrode, 2048, 1 $\mu$V, first dorsal interosseous—hand area electrode, 2048, 1 $\mu$V, little finger—hand area electrode, 1024, 2 $\mu$V

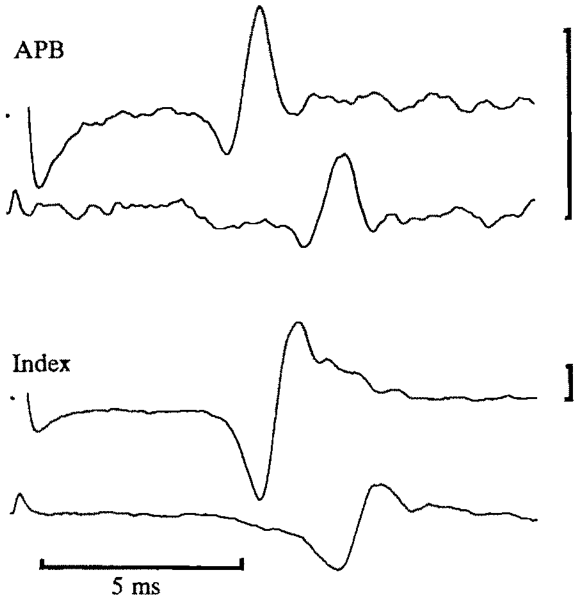

FIG 3 Peripheral nerve potentials in 1 subject produced by motor-point stimulation of abductor pollicis brevis (*top traces*) and stimulation of the digital nerves of the index finger (*bottom traces*). The upper trace in each pair represents the volley recorded at the elbow and the lower trace the volley recorded at the axilla. Potentials were recorded using needle electrodes. Stimuli were delivered at the onset of the traces. The conduction velocity for the most rapidly conducted afferents in each volley was 68–70 $m \cdot s^{-1}$. Averages of 2048 responses. Vertical calibration 0.5 $\mu V$.

dorsal interosseous compared with the median fascicle innervating abductor pollicis brevis. This suggestion was confirmed in 2 subjects in whom the latency of N1 following stimulation within abductor digiti minimi was 0.8–1.0 ms less than with stimulation within first dorsal interosseous. The latency to N1 for motor-point stimulation of abductor pollicis brevis was between that for stimulation of the digital nerve of the index and that for stimulation of the median nerve at the wrist (fig. 1). This is compatible with a similar conduction velocity for the fastest cutaneous and muscle afferents from the hand (Gandevia *et al.*, 1984; *see also* fig. 3).

Limited mapping with a montage of 4 scalp recording sites suggested that there was a somatopic organization of the cerebral projection from different muscles. However, the initial components of the cerebral potential were commonly recordable from all 3 contralateral scalp electrodes (fig. 4). The initial N1-P1 component for intrinsic hand muscles was usually largest at the 'hand area' electrode (electrode 3) or the 'anterior' electrode (electrode 2A). For extensor digitorum communis and flexor carpi radialis the N1-P1 component was usually of maximal amplitude at the 'intermediate' or 'anterior' site (electrodes 2 and 2A, respectively).

Examples of the potentials from deltoid in 3 subjects are shown in fig. 5. The cerebral potential recorded for anterior deltoid usually showed a wide distribution with the initial components largest at the 'intermediate' electrode or, in 1 subject, nearer the vertex. Before the initial negativity at a mean latency of 15.0 ms there was an earlier positivity (by 3–4 ms) in 4 of the 6 subjects. Presumably this widespread positivity represented a far-field subcortical component.

In 2 subjects there was difficulty in obtaining the cerebral potential to stimulation

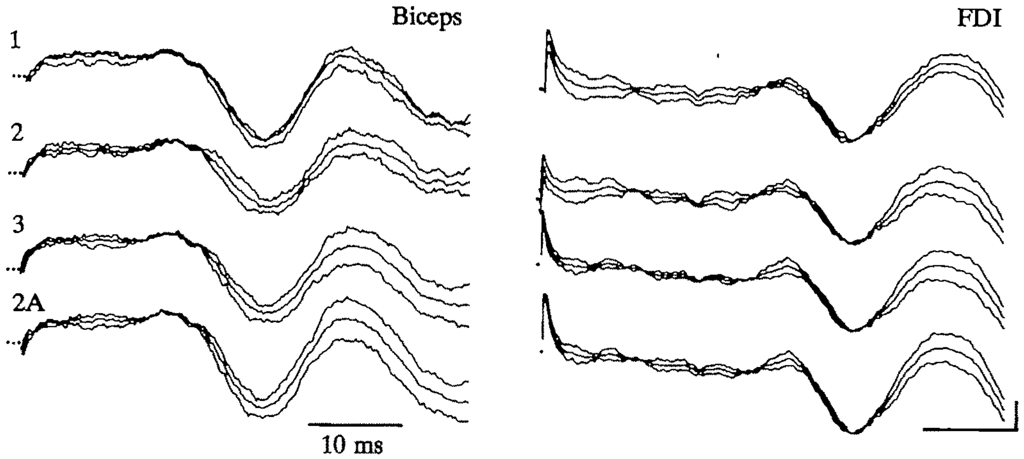

FIG. 4. Cerebral potentials produced by motor-point stimulation of biceps brachii (*left*) and first dorsal interosseous (*right*). Data from 1 experiment Traces from each muscle are shown for 4 electrode sites with the reference on the contralateral earlobe. The electrode sites are described fully in Methods. 1: vertex; 3· hand area; 2· 'intermediate' between 1 and 3, and 2A. anterior. Averages of 2048 responses. Vertical calibration· 0.5 $\mu$V.

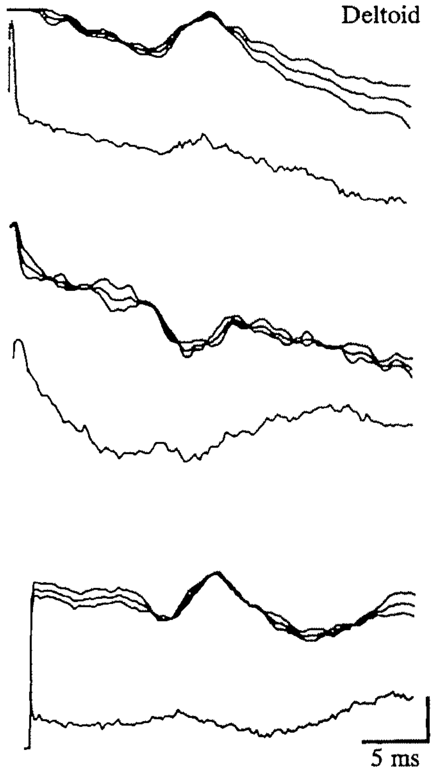

FIG. 5. Cerebral potentials in 3 subjects produced by stimulation of the motor point of the anterior deltoid. The upper set of 3 superimposed traces for each subject contains 2 averages and the mean of the 2 averages. These responses are recorded from the anterior electrode using the earlobe reference (*see* Methods). The lower single traces for each subject show a bipolar derivation between the anterior electrode and the vertex electrode. Averages of 1024–2048 responses. Vertical calibration for the duplicate averages (from upper traces downwards): 0.5 $\mu$V, 0.5 $\mu$V, 0 7 $\mu$V.

of biceps brachii. To check that the intramuscular stimuli did indeed activate group I afferent fibres, stimulus intensity was reduced and stimuli were delivered during a weak voluntary contraction, so allowing the short-latency spinal reflex response in homonymous motoneurons to be identified in the averaged EMG (fig. 6). The latency of this H reflex in biceps brachii was 11–13 ms. Because a relatively small muscle afferent volley can produce cerebral potentials of near maximal amplitude (Gandevia *et al.*, 1982), the inability to define a cerebral potential presumably reflects a poor signal-to-noise ratio at the recording electrodes rather than failure to activate afferent fibres. After failure to document cerebral responses to stimulation of biceps brachii, the studies were repeated on another day and clear cerebral potentials were identified.

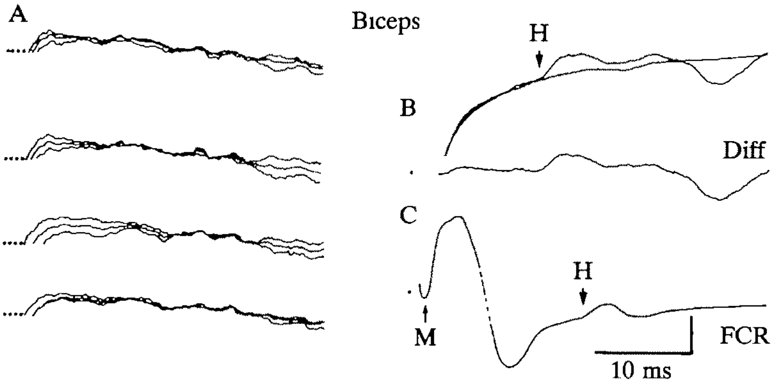

FIG 6. A, cerebral potentials produced by motor-point stimulation of biceps brachii Data from one study in which no definite cerebral potential was recorded. The sequence of electrode sites is the same as for fig 3. Averages of 2048 responses. Vertical calibration. 0 7 $\mu$V B, H reflex evoked by motor-point stimulation at close to motor threshold. The lowest trace ('Diff') is the difference between the upper two traces, i.e. the responses obtained during a weak voluntary contraction and when the muscle was relaxed The H reflex during a voluntary contraction occluded when stimulus intensity was increased Upper traces are averages of 32 responses Vertical calibration: 0.2 mV C, H reflex evoked by motor-point stimulation of flexor carpi radialis (FCR) during a weak voluntary contraction The reflex response occluded when the stimulus intensity was increased. Average of 16 responses Vertical calibration 1 5 mV The cerebral potentials produced in this subject by similar stimuli is shown in fig 2

The amplitude of the initial N1-P1 component did not vary significantly between the different muscles of the upper limb (Table). This seemed surprising given the conventional view that the sensorimotor cortex is devoted particularly to representations of distal muscles (*see* Discussion). In 2 subjects the cerebral potential recorded from stimulation of deltoid was a simple waveform consisting of one major negativity during the first 50 ms, that is, it appeared to lack the common W-shaped pattern (fig. 2; *see also* Giblin, 1964).

In addition to the muscles studied in detail, a cerebral projection with similar properties to those described above was noted for other muscles in the hand (abductor digiti minimi), forearm (flexor digitorum sublimis, extensor indicis, extensor carpi radialis) and upper arm (triceps brachii).

### *Intersubject variability in the cerebral potential*

In the above studies long recording sessions were undertaken with subjects familiar with the stimulation and recording procedures. Studies were therefore performed on a further 5 subjects who had not previously participated in evoked potential experiments. In each subject the projection from abductor pollicis brevis was analysed. No special precautions were taken to ensure optimal relaxation of the subject. The first 2 duplicate averages (of 512–2048) responses from each subject are shown in fig. 7. That a potential was evident could be determined from averages of as few as 256 responses although greater numbers of responses were required to measure accurately the latency and amplitude of the potential. In 1 subject who had difficulty in relaxing scalp musculature, the projection was not clearly defined even after 2048 sweeps (fig. 7, fourth traces).

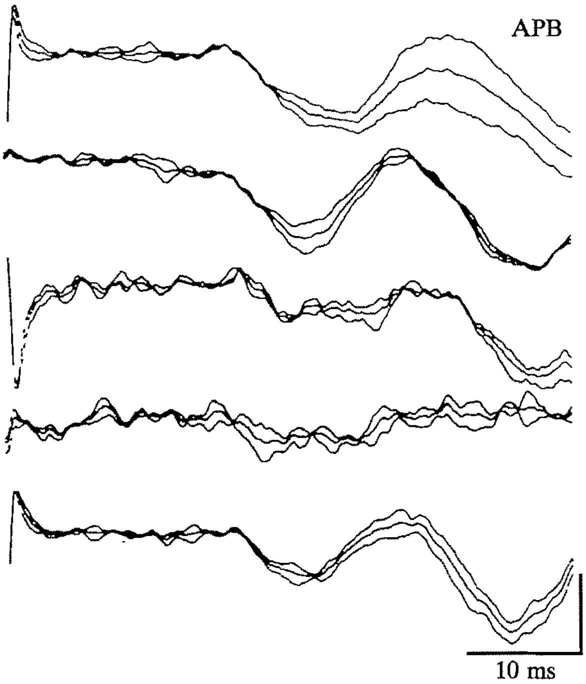

FIG 7. Cerebral potentials produced in 5 subjects who were not familiar with recording or stimulation techniques Each set of traces from 1 subject All averages obtained with motor-point stimulation of abductor pollicis brevis (APB) at 2–3 times the motor threshold The number of responses in each average and the vertical calibration are given for each subject from top traces downwards n = 1024, 1 μV, 1024, 3 μV; 1024, 1 μV, 2048, 0.6 μV; 1024, 2 μV.

## DISCUSSION

By stimulation within motor nerve fascicles the technique of microneurography has previously been used to document the cortical projection of muscle afferents from intrinsic muscles of the hand (Gandevia *et al.*, 1984; Gandevia, 1985) and foot (Burke *et al.*, 1981, 1982; Starr *et al.*, 1981). Because this technique is inappropriate for nerve fascicles innervating proximal muscles or for diagnostic studies, the technique of motor-point stimulation with an insulated microelectrode has been used. It has revealed, in particular, a rapidly conducting projection from individual *proximal* muscles in addition to that for individual intrinsic muscles of the hand. Before some implications of the findings are considered there is a discussion of the afferent fibres responsible for the cerebral potentials.

There are a number of reasons for the view that the fibres responsible for the cerebral projection are probably group I muscle afferents. First, the cerebral potentials could be obtained at stimulus levels close to threshold for motor axons. This stimulus level favours activation of large diameter afferent fibres. The conduction velocity of the initial component of the afferent volley produced by motor-point stimulation of distal muscles was rapid, consistent with findings obtained using microneurography (Gandevia *et al.*, 1984). In addition, the latency of the initial component of the cerebral potentials is short, given that for stimulation of the parent mixed nerve trunk. Secondly, while afferents innervating receptors outside muscle can run in muscle fascicles or motor nerves, such contamination is not likely to be frequent, particularly at the level of the motor point (e.g., Barker, 1962; Matthews, 1972). Indeed 'contamination' should be less at the motor point than at more proximal levels within the nerve fascicle (or fascicles) which innervates the muscle. Pacinian corpulses occur rarely within muscle, while the more numerous paciniform receptors are usually (but not always) innervated by small diameter axons (Stacey, 1969; *see also* Sathian and Devanandan, 1983, Richmond and Stuart, 1985). Thirdly, a study in subhuman primates suggests that afferents innervating secondary spindle endings, pacinian and paciniform endings are of smaller diameter than those of primary spindle endings and Golgi tendon organs (Devanandan *et al.*, 1980). Even if, as revealed by Devanandan *et al.* (1980), Ib afferents are marginally smaller in diameter than group Ia afferents it is likely that the intramuscular stimuli activated both categories of group I afferents, in the majority of studies. However, it is not yet established that Ib afferents project to the human cerebral cortex although such a projection exists in the cat (McIntyre *et al.*, 1984). At least for distal muscles there is combined electrophysiological and psychophysical evidence for a cortical projection from primary spindle endings (Gandevia, 1985). Furthermore, intrinsic muscles of the hand contain relatively few tendon organs (Devanandan *et al.*, 1983). Fourthly, the stimuli which evoked the cerebral potentials did not produce local skin sensations or cutaneous paraesthesiae. In addition, the single stimuli did not produce sharp localized sensations referred to the joints. Such sensations are evoked by intrafascicular microstimulation of afferents which innervate joints (Macefield *et al.*, 1987; *see* Gandevia, 1985). It is concluded that group I muscle afferents are activated by the selective stimulation at the motor point and that they give rise to the initial component of the observed cortical potentials.

The main early component of the cerebral potential for distal muscles (equivalent to N19 for stimulation of the median nerve at the wrist) was largest at recording sites more lateral on the scalp whereas for biceps brachii and deltoid this component was often larger closer to the vertex. These findings are consistent with those obtained for direct mapping of human sensorimotor cortex using directly recorded cortical potentials (Woolsey *et al.*, 1979) or electrical stimulation (Penfield and Boldrey, 1937). Psychophysical studies support a role for muscle afferents from proximal muscles of the upper limb in kinaesthesia (Goodwin *et al.*, 1972; Hall and McCloskey, 1983). Muscle afferents from the lower limbs produce a cerebral potential which is maximal near the vertex (e.g., Tsumoto *et al.*, 1972; Starr *et al.*, 1981; Cruse *et al.*, 1982). This has been confirmed by stimulation of abductor hallucis and tibialis anterior (S. C. Gandevia, unpublished observations).

In 2 subjects the cerebral potential produced by muscle afferents from the deltoid was of comparatively simple morphology. This may reflect a genuine difference in the strength and or topography of the projection of afferents from proximal muscles, but it may also be due to the shorter conduction path (and hence reduced afferent dispersion) for the afferent volley evoked at the motor point of proximal muscles. It is difficult to use the data from this study to quantify the potency of connections between the group I afferents of the various muscles and the sensorimotor cortex because it may depend on a number of physiological variables (afferent dispersion, properties or relay nuclei) and technical factors (dipole orientation, relative site of stimulation, etc.). Nevertheless, it is notable that the size of the cerebral potentials was similar for all muscles studied in the upper limb. Given that the intrinsic muscles of the hand contain only about one-tenth the number of muscle spindle endings than the larger proximal muscles in the human upper limb (Buchthal and Schmalbruch, 1980), the projection strength from individual group I afferents may be greater for distal than proximal muscles. If the somatotopic patterns are less well defined for the muscle than the cutaneous afferent projection (Kaas, 1983), it may explain the relatively wide distribution and similar amplitude of the individual muscle afferent potentials in the present study.

The technique of intramuscular stimulation used in this study has a number of potential clinical applications. First, it can be adapted to obtain H reflexes from proximal muscles (fig. 6). Secondly, it provides an additional method to assess particular nerve roots either with H reflexes or cortical evoked potentials. Thirdly, the cortical potentials evoked by intramuscular stimuli allow assessment of the central pathways which convey muscle afferent inputs to the cerebral cortex independently of those pathways which convey cutaneous afferents. One disadvantage of the technique is that the size of the cerebral potentials produced is relatively small, and may be difficult to define in an occasional patient. Given the number of motor and sensory fascicles within the median and ulnar nerves (at wrist level) the amplitude of the cerebral potential produced by single cutaneous (Gandevia and Burke, 1984) and motor fascicles (present study) is larger than would be expected if potentials from each fascicle were added algebraically. This apparent 'saturation' of the cerebral potential presumably reflects the effect of neural occlusion at levels up to, and including, the somatosensory cortex (Gandevia and Burke, 1984; *see also* Zarzecki and Wiggin, 1982). However, cortical potentials from single intrinsic muscles can usually be detected, even in subjects unfamiliar with the procedure (fig. 7). The detection of a cortical projection from low-threshold muscle afferents raises questions about the selectivity of the afferent volleys generated using 'dermatomal' stimulation (e.g. Jörg *et al.*, 1982; Eisen, 1982, 1986). Whether or not there is a twitch contraction of underlying muscles, dermatomal stimulation could elicit an afferent volley that is contaminated by muscle afferents.

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# PATTERNS OF CONDUCTION FAILURE IN THE GUILLAIN-BARRÉ SYNDROME

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## SUMMARY

Within the limits of the Guillain-Barré syndrome, the pattern of clinical deficit is variable. Motor deficit may begin proximally or distally in the extremities and sensory deficit is sometimes, but not always present. Longitudinal studies were performed in 13 patients, starting during the progressive phase. The severity of the clinical deficit was related to the amplitude of the compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs). Two patterns were detected, but could only be reliably distinguished during the progressive phase of the disease. (1) A length-dependent reduction of the CMAP, i.e., a progressive decrease of the CMAP on moving the stimulating electrode to more proximal stimulation sites This could often be attributed to conduction block. In this pattern (Group A), the sensory potentials were spared with only 1 exception. These patients had motor involvement without sensory deficit and the myotatic reflexes could be preserved up to MRC grade 3 paresis. (2) A simple reduction of the CMAP, i.e., the amplitude decreased during clinical deterioration, but during a single investigation remained similar for stimulation at all levels of the nerve. In this pattern (Group B), motor and sensory fibres were similarly involved. These patients showed both motor and sensory deficit and early myotatic areflexia The second pattern might be explained by an immunological mechanism with a predilection for those regions of the peripheral nervous system where the blood-nerve barrier is naturally deficient. In the first pattern the discrepancy between the involvement of motor and sensory fibres raises new questions, the solution of which might be of importance for the understanding of the Guillain-Barré syndrome

## INTRODUCTION

The acute Guillain-Barré Syndrome (GBS) is characterized by a progressive flaccid paresis with reduction or loss of tendon reflexes, followed by functional recovery in the majority of patients. Several other features support the diagnosis (*see* Asbury, 1981). Within these limits, the clinical pattern is variable. The paresis may start proximally or distally in the limbs. Sensation is involved in some patients; in others it is normal despite severe paresis. Weakness may begin in the cranial nerves and spread downwards. Inflammatory demyelinating lesions scattered throughout the peripheral nervous system are considered to be responsible (Asbury *et al.*, 1969).

An important pathophysiological hallmark is slowing of conduction, but this is

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not related to the severity of the disease (McLeod, 1981). Decreased compound muscle action potentials (CMAPs), as evidence of conduction failure, accompany the motor deficit (Lambert and Mulder, 1964; Brown and Feasby, 1984; Albers *et al.*, 1985; Feasby *et al.*, 1985; Mills and Murray, 1985). In a recent study, Brown and Feasby (1984) stressed the occurrence of conduction block, that is, loss of conduction in axons between two stimulation sites. In addition, they often found very low amplitudes with distal stimulation suggestive of distal conduction failure. They did not, however, describe how these two phenomena were related in individual patients.

Sensory deficit, in contrast to paresis, is variably present in GBS patients. There are two factors which might be responsible for this. (1) A wide fibre spectrum serves sensory function, both myelinated and unmyelinated; therefore, any disease with fibre type predilection will leave many sensory fibres unaffected. (2) Sensory fibres may be spared in some patients despite involvement of motor fibres. In this context, the recent emphasis on the variability of sensory conduction studies in the GBS syndrome compared with other polyneuropathies is noteworthy (Murray and Wade, 1980; Albers *et al.*, 1985).

In this study we compared the clinical course with the pathophysiological changes in 13 consecutive patients. We sought evidence both for conduction block and distal conduction failure in the peripheral motor and sensory system.

## PATIENTS AND METHODS

Thirteen consecutive patients were studied. They were included in the study if they (1) fulfilled the GBS criteria (Asbury, 1981) and (2) were still deteriorating. Their clinical deficit at the nadir varied: 2 patients had difficulty in walking, 7 were chairbound or bedridden and 4 required artificial ventilation. In all patients, median and peroneal nerves were investigated by stimulation at the wrist and elbow, and at the ankle and knee (the neck of fibula), respectively. The average number of studies was 9 (range 2–33). A Disa 15-c-01 electromyograph was used.

Motor fibres were studied by recording with surface clip electrodes from the abductor pollicis brevis (APB), tibialis anterior (TA) and extensor digitorum brevis (EDB) muscles. Sensory fibres were examined by recording antidromically from the index finger; motor and sensory responses on median nerve stimulation were recorded simultaneously. Care was taken to place the active electrode at the optimal site for a biphasic maximal compound muscle action potential (CMAP).

The sensory nerve action potentials (SNAPs), the CMAPs and 12–20 trials for F waves were recorded on paper; the latencies and peak-peak amplitudes were measured. The duration of the negative phase of the CMAP was measured to study differential dispersion. For APB, differential dispersion was defined as an increase in duration of the negative peak by more than 8%, when stimulation was carried out at the elbow rather than at the wrist (Brown and Feasby, 1984). Nerves were stimulated supramaximally with rectangular pulses of 0.3 ms duration. Submaximal stimulation strength was used to locate the optimal stimulus electrode site. In some instances, more proximal levels of the median nerve were stimulated, taking care not to stimulate the ulnar nerve. If the distal SNAP remained normal, somatosensory evoked potentials (SEPs) of both median nerves were obtained.

Needle electromyography was performed in 9 patients. It was omitted in 3 adults and 1 child for fear of losing their cooperation for the remainder of the study.

## RESULTS

### *The progressive phase of the disease*

At the nadir of the disease, a decrease in CMAPs was observed in all patients when compared with earlier studies or with data at the stage of late recovery (Table 1). In all patients this was uniform in APB, TA and EDB. Fig. 1 illustrates the reduction in CMAP amplitude related to general clinical deterioration. Stimulation at different levels of the nerve, however, showed different patterns of CMAP reduction. In 7 patients, the amplitude decreased when the stimulus electrode was moved to more proximal sites. In APB, between wrist and elbow stimulation, the decrease in amplitude ranged from 1.6–11.7 mV (Table 1, Group A). Axilla stimulation, tested in 5 of these patients, showed a further decrease in the CMAP. Furthermore, the amplitude obtained on wrist stimulation was relatively large, although in all patients, it was lower than the amplitude measured early in the course of the disease or after recovery. We have referred to this pattern descriptively as a *length-dependent reduction*. Fig. 2, Case A1, demonstrates how the potentials evoked by wrist and elbow stimulation were related during clinical deterioration; original recordings are presented in fig. 3. In this group, differential dispersion was seen in 3 patients at the nadir of the disease (Table 2).

TABLE 1 MRC SCORE AND COMPOUND MUSCLE ACTION POTENTIALS (mV) FOR ABDUCTOR POLLICIS BREVIS

| | *First measurement** | | | *Nadir* | | | *Recovery (partial)* | | | *Recovery (late)* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Case* | *MRC score* | *Wrist stim* | *Elbow stim* | *MRC score* | *Wrist stim* | *Elbow stim* | *MRC score* | *Wrist stim* | *Elbow stim* | *MRC score* | *Wrist stim* | *Elbow stim* |
| A1 | 3 | 17.5 | 14.0 | 0 | 12.5 | 0.8 | 3 | 7.5 | 0.5 | 4 | 9.0 | 7.5 |
| 2 | 4 | 7.2 | 4.7 | 4 | 7.2 | 4.7 | 4 | 8.0 | 5.2 | 5 | 15.0 | 13.5 |
| 3 | 2 | 8.0 | 4.0 | 0 | 2.0 | 0.3 | 3 | 4.2 | 3.8 | 4 | 9.6 | 9.0 |
| 4 | 2 | 7.6 | 2.0 | 2 | 7.6 | 2.0 | | | | 5 | 11.5 | 11.5 |
| 5 | 4 | 12.0 | 8.0 | 3 | 7.4 | 2.2 | 4 | 12.0 | 4.0 | 5 | 13.5 | 11.5 |
| 6 | 2 | 8.2 | 0.9 | 0 | 7.6 | 0.75 | 1 | 0.5 | 0.4 | ** | ** | ** |
| 7 | 4 | 8.4 | 6.8 | 4 | 8.4 | 6.8 | 4 | 9.6 | 6.4 | 5 | 12.5 | 12.5 |
| B1 | 4 | 2.1 | 2.2 | 4 | 2.1 | 2.2 | | | | 5 | 11.8 | 12.0 |
| 2 | 4 | 2.9 | 2.9 | 4 | 2.8 | 2.7 | 4 | 4.5 | 3.4 | 5 | 9.6 | 9.4 |
| 3 | 4 | 10.5 | 10.0 | 3 | 1.7 | 1.5 | 4 | 4.4 | 4.0 | 5 | 16.0 | 15.0 |
| 4 | 4 | 6.3 | 6.3 | 3 | 1.9 | 1.7 | 4 | 6.4 | 4.8 | 5 | 14.5 | 13.8 |
| 5 | 1 | 0.1 | 0.1 | 1 | 0.1 | 0.1 | 3 | 0.7 | 0.6 | 4 | 11.2 | 9.7 |
| 6 | 3 | 4.1 | 4.1 | 2 | 2.4 | 1.7 | 4 | 1.2 | 0.8 | 5 | 14.0 | 12.5 |

* If the first measurement was performed at about the nadir, it is repeated in the column labelled 'nadir' ** Not yet recovered

In the remaining 6 patients, there was no reduction in amplitude between the wrist and elbow, or this was only minimal ($<0.7$ mV). (Table 1, Group B). This was also true for more proximal segments, studied additionally in 4 patients. On wrist stimulation, these patients showed low amplitudes compared with patients in Group A (Table 1). We have given this pattern the descriptive title *simple reduction*.

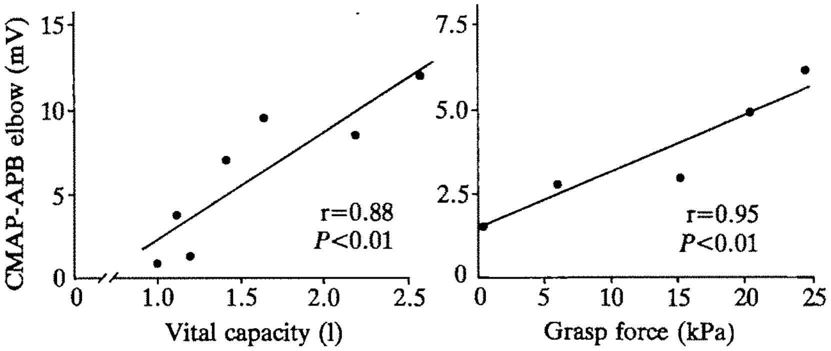

FIG 1 Relationship between clinical deterioration and decrease in the peak-peak amplitude of the CMAP of APB in *Cases A1* (*left*) and *B4* (*right*)

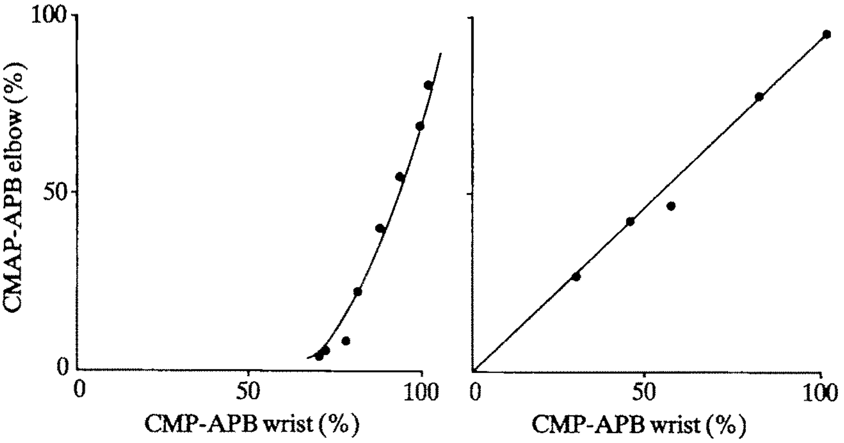

FIG. 2 Relationship between the CMAP of APB after wrist and elbow stimulation during clinical deterioration. The CMAPs are proportional to the first measured CMAP after wrist stimulation. Note that the first measurement is at the right top corner *Case A1* (*left*), *Case B4* (*right*).

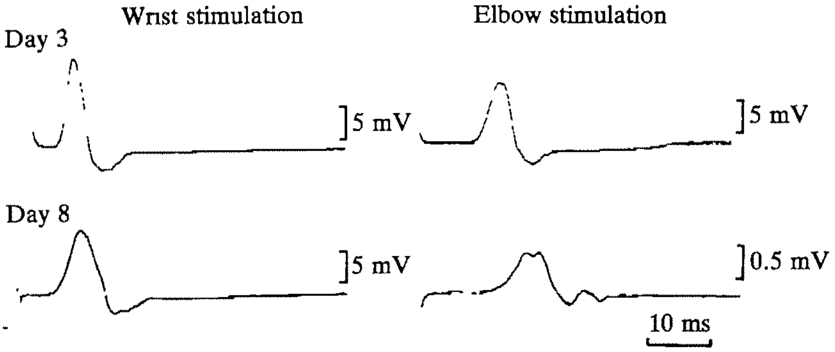

FIG. 3. CMAPs from APB in *Case A1*. The amplitudes decrease between days 3 and 8 of the disease but most prominently with elbow stimulation (length-dependent reduction) Note the different voltage calibration for elbow stimulation at day 8

TABLE 2. MOTOR CONDUCTION STUDIES OF THE MEDIAN NERVE (APB) AT THE NADIR

| *Case* | *DML* (<3.7 *ms*)* | *NCV* (>51 *m·s*$^{-1}$)* | *Differential dispersion* | *F Response wrist* (<32 *ms*)* |
|---|---|---|---|---|
| A1 | 1.9 | 44 | + | — |
| 2 | 3.2 | 60 | − | 33.4 |
| 3 | 5.2 | 34 | − | — |
| 4 | 3.4 | 54 | + | 35.9 |
| 5 | 2.8 | 49 | + | — |
| 6 | 3.0 | 62 | − | — |
| 7 | 3.4 | 51 | − | — |
| B1 | 10.6 | 57 | − | 45.0 |
| 2 | 16.9 | 41 | − | — |
| 3 | 7.2 | 64 | − | 42.3 |
| 4 | 8.3 | 61 | − | — |
| 5 | 26.2 | 32 | − | — |
| 6 | 8.9 | 39 | − | 54.0 |

*Normal values. DML = distal motor latency NCV = nerve conduction velocity.

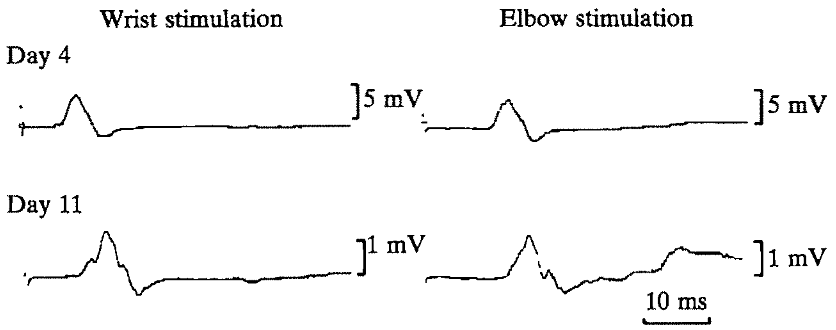

FIG. 4. CMAPs from APB in *Case B4*. The amplitudes decrease between days 4 and 11 after the onset of the disease. There is no difference in the size of the amplitudes obtained with wrist or elbow stimulation (simple reduction)

In fig. 2, Case B4, this pattern is demonstrated by the linear relationship between the amplitudes obtained on wrist and elbow stimulation; original recordings are presented in fig. 4. The CMAP for EDB was often too low to allow any pattern to be distinguished, but if CMAP deterioration could be followed during clinical progression, the pattern was similar to that for the median nerve (fig. 5).

Conduction studies at the nadir are given in Table 2. There was a marked increase in the distal motor latency in Group B compared with Group A. Also proximal to the elbow, conduction was slow in Group B, since the distal motor latencies alone were not sufficiently prolonged to explain the long latencies of the F responses.

### *The sensory system*

Sensory signs were present in all patients in Group B (Table 3), with the exception of Case B1, a moderately affected child aged 7 yrs. In all others, two-point

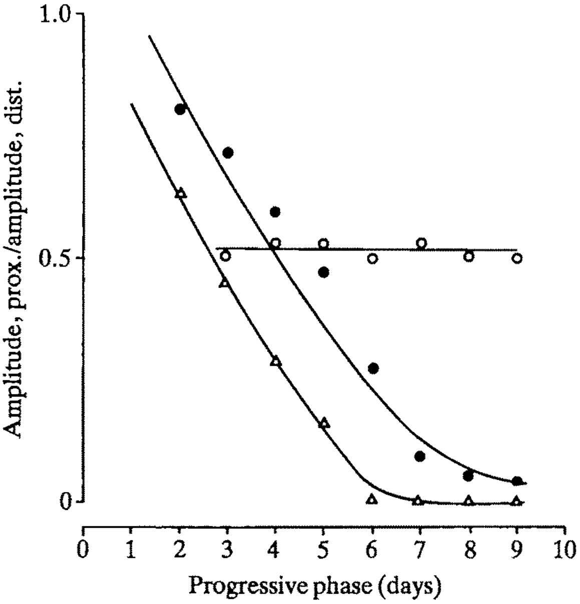

FIG 5. Ratio of amplitudes with elbow and wrist stimulation and knee and ankle stimulation obtained during clinical deterioration in *Case A1* A length-dependent amplitude reduction is characterized by a decrease in the ratio as seen in the motor fibres of the median and peroneal nerves. No length-dependent reduction can be observed in the sensory fibres of the median nerve. For sensory nerves a ratio of 0 5 is within normal limits, the normal ratio for motor nerves is above 0 9 (Kimura *et al.*, 1986). CMAP-APB (full circles), CMAP-EDB (open triangles), SNAP-second digit (open circles)

TABLE 3 SENSORY FUNCTION CLINICAL AND PHYSIOLOGICAL STUDIES ON THE MEDIAN NERVE

| | *Nadir* | | | *Recovery (late)* | | | | |
|---|---|---|---|---|---|---|---|---|
| *Case* | *Clinical deficit (2nd digit)* | *SNAP (μV) wrist stim* | *SNAP (μV) elbow stim* | *Clinical deficit (2nd digit)* | *SNAP (μV) wrist stim* | *SNAP (μV) elbow stim* | *SSEP wrist stim* | *Reflexes present up to paresis grade 3 (MRC)* |
| A1 | — | 36 | 18 | — | 52 | 24 | Not done | + |
| 2 | — | 56 | 28 | — | 54 | 32 | Normal | + |
| 3 | + | 0 | 0 | — | 7 | 5 | Not done | — |
| 4 | — | 13 | 8 | — | 11 | 7 | Normal | — |
| 5 | — | 10 | 6 | — | 15 | 7 | Normal | — |
| 6 | — | 20 | 15 | * | * | * | Normal | + |
| 7 | — | 13 | 6 | — | 13 | 7 | Normal | — |
| B1 | ? | 0 | 0 | — | 38 | 29 | | — |
| 2 | + | 0 | 0 | — | 0 | 0 | | — |
| 3 | + | 0 | 0 | — | 8 | 5 | | — |
| 4 | + | 0 | 0 | — | 13 | 10 | | — |
| 5 | + | 0 | 0 | — | 4 | 0 | | — |
| 6 | + | 0 | 0 | — | 30 | 20 | | — |

* Patient not yet recovered.

discrimination deteriorated beyond 5 mm, position sense was disturbed, and there was a decrease in touch and pain sensation. In all patients in this group, the sensory potential from the index finger disappeared as the disease progressed (Table 3, fig. 6). Six of 7 patients in Group A, however, had no clinical sensory deficit, and the sensory potential was spared (Table 3), despite a severe decrease in the CMAP in

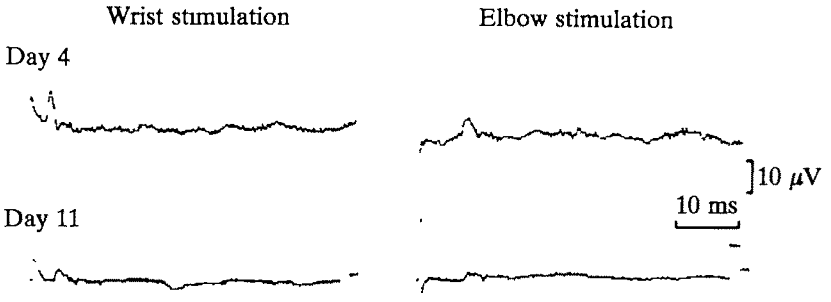

FIG. 6. SNAPs from the second digit in *Case B4* The initial amplitude was small and the potential disappeared at day 12 of the disease

the same nerve segment (Table 1). The clearest evidence of this discrepancy can be seen in fig. 5. It illustrates the loss of amplitude over the lower arm and lower leg, respectively, during disease progression. Between the elbow and wrist the motor fibres became progressively blocked, whereas the adjacent sensory fibres were not affected. Fig. 7 presents original SNAPs; some amplitude decrease can be seen, due to dispersion in the region of the carpal tunnel. In this patient, sensory signs were absent despite total paralysis of the extremities. This was in sharp contrast to patients from Group B with a comparable motor deficit; in these patients, sensory deficit was sometimes so severe that they hardly noticed their legs being moved.

The differences between Groups A and B with respect to clinical sensory deficit and the presence or absence of a sensory potential at the nadir are statistically significant ($P=0.02$ and 0.004, respectively, Fisher exact test). Three patients in Group A had preserved reflexes up to MRC grade 3 paresis (Table 2). In all patients of Group A tested with SEPs, proximal sensory conduction was also normal (Table 3). The sparing of sensory fibres in Group A was also reflected in the electrical excitability. Stimulation of motor fibres usually became very critical with regard to stimulation site, and often over 20 mA of stimulus strength was necessary to produce a maximal CMAP. Maximal sensory fibre activation, however, was always obtained easily in patients in Group A with the exception of Case A3.

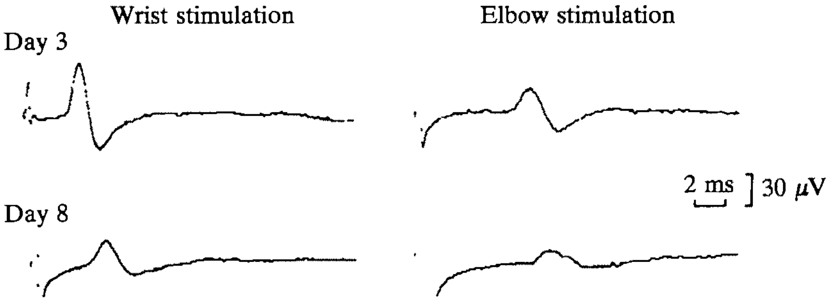

FIG 7 SNAPs from the second digit in *Case A1*. Dispersion occurred distally from the wrist This led to some decrease in the amplitudes without a clinical sensory deficit.

### *The plateau phase and recovery*

During the plateau phase and during early recovery, the CMAPs showed a further decrease in 3 patients (Table 1). In Cases A1 and B6 this was paralleled by increasing dispersion. In Case A6 it was caused by extensive axonal degeneration, evidenced by abundant denervation potentials in APB and other muscles tested. During this phase of denervation there was no change in motor conduction velocity, nor in sensory conduction. In Group B the majority developed some 'length-dependent reduction' of the CMAP during early recovery (Table 1).

At later stages of recovery, CMAP amplitudes always increased and amplitude reduction between wrist and elbow diminished or disappeared (Table 1). In general it was observed that recovery was not always a simple mirror image of the progressive phase. Amplitudes after wrist stimulation tended to be more variable between measurements, as did the CMAP decline between wrist and elbow.

### *Needle electromyography (EMG)*

Needle EMG was performed in 9 of 13 subjects. In Group A, 4 of 6 tested patients showed signs of denervation and/or reinnervation. Denervation potentials were particularly abundant in Cases A3 and A6. These 2 patients showed prolonged plateau phases and slow recovery over many months compared with the other subjects in this group. In Group B, 4 of 6 patients were tested; in Case B5, who was severely affected, many polyphasic potentials were found in her prolonged recovery phase. Cases B2, B3 and B6 were tested during progression and recovery. Case B2 showed a few positive denervation and fibrillation potentials in APB at the nadir and none during recovery; no polyphasic potentials could be detected at the final examination. Case B3 showed no signs of denervation during progression or during recovery. In Case B6 sparse fibrillation potentials but no positive denervation potentials were seen during the progressive phase, and no increase of polyphasic potentials in the recovery phase.

## DISCUSSION

In a longitudinal study of 13 GBS patients, we confirmed earlier findings that slowing of conduction (McLeod, 1981) and decrease of action potential amplitudes (Lambert and Mulder, 1964; Brown and Feasby, 1984; Albers *et al.*, 1985; Feasby *et al.*, 1985; Mills and Murray, 1985) and, to a variable extent, axonal degeneration (Brown and Feasby, 1984; Feasby *et al.*, 1986), are important pathophysiological characteristics of the GBS syndrome. In addition, we were able to distinguish two different pathophysiological patterns, one characterized by a length-dependent reduction of the CMAP, the sensory system usually being spared (Group A), the other by simple CMAP reduction with similar involvement of the sensory system (Group B). Both patterns are illustrated schematically in fig. 8.

Group A was characterized by a length-dependent reduction of the CMAP, that is, the CMAP decreased when the stimulus electrode was moved from distal to

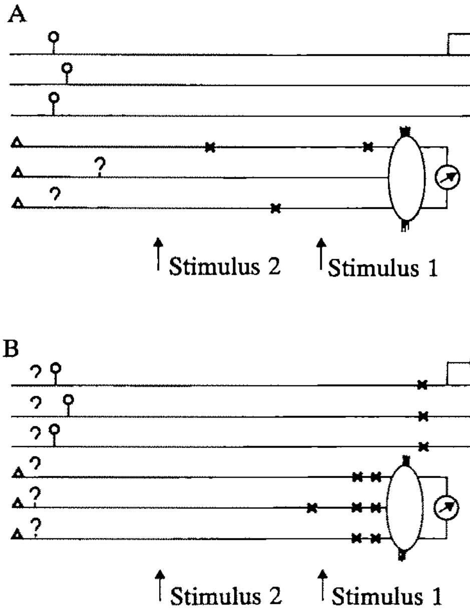

FIG. 8. Schematic illustration of the pathophysiological patterns in Groups A (A) and B (B). Crosses indicate lesions detected in this study and question marks hypothetical lesions *See* text for further discussion

more proximal stimulation sites. In 6 out of 7 patients in this group, the SNAP was spared, and the SEP, performed in 5, was also normal (fig. 8A). Clinically this pattern consisted of a flaccid tetraparesis with normal sensory function in all but 1 patient. Normal sensory function included Ia muscle afferents in at least 3 patients, evidenced by the persistence of myotatic reflexes up to MRC grade 3 paresis.

A length-dependent reduction of the CMAP is an indication that the lesions are scattered along the segment of the nerve studied. It may be caused by conduction block or by slowing of conduction leading to dispersion and phase cancellation of individual motor unit potentials (Lee *et al.*, 1975; Lewis *et al.*, 1982; Brown and Feasby, 1984; Mills and Murray, 1985). In the absence of an excessive increase in the duration of the negative phase of the action potential with stimulation at several sites, the reduction in amplitude can be ascribed to conduction block (Brown and Feasby, 1984); this was true for 4 patients in Group A. If, however, the reduction in amplitude is very substantial, conduction block is very likely, even in the presence of some temporal dispersion (Lewis *et al.*, 1982); this was the case in the remaining 3 patients (Cases A1, A4, A5). Conduction block was not restricted to the forearm segment of the nerve. It was also present in more proximal parts of the nerve trunk, as already described by others (Brown and Feasby, 1984; Mills and Murray, 1985).

Group B was characterized by a simple decrease in the CMAP during clinical deterioration, that is, the CMAP was very similar for all levels of nerve stimulated. In this pattern, motor and sensory fibres are similarly affected (fig. 8B). Clinically, these patients had a flaccid tetraparesis associated with low CMAP size, sensory deficit and early areflexia.

The decrease in the CMAP during clinical deterioration without conduction block between stimulation sites could be explained by two mechanisms: either axonal degeneration or conduction block caused by demyelination in the distal part of the nerve. On the basis of the CMAP decrease alone, these two mechanisms are not distinguishable. Additional information, however, favours distal demyelination, especially the excessive increase in distal motor latency (Table 2) and the relative absence of denervation potentials. Rapid clinical recovery, seen in some of these patients, further excludes axonal degeneration of whole motor fibres, although it does not exclude degeneration of terminal branches.

The two patterns described are not necessarily mutually exclusive; overlap may occur as illustrated by Case A3, who showed involvement of the sensory fibres comparable to patients in Group B. Nevertheless the two patterns so often occur separately in individual patients that they may be of help in the study of pathogenesis. Recently a humoral pathogenetic mechanism has received more support by the demonstration of (1) a demyelinative effect of GBS serum in vivo (Feasby *et al.*, 1982; Saida *et al.*, 1982; Harrison *et al.*, 1984), (2) the presence in all GBS patients of complement-fixing antibodies directed against peripheral nerve (Koski *et al.*, 1986) and (3) a positive effect of plasma exchange on the course of the disease (Osterman *et al.*, 1984; Guillain-Barré Study Group, 1985). A humoral pathogenetic factor would be predicted to have a predilection for those regions of the peripheral nervous system where the blood-nerve barrier is naturally deficient, namely, according to Olsson (1984), the distal parts of the nerves, the dorsal root ganglia and possibly the spinal roots. This distribution is consistent with the findings in Group B (fig. 8B). Initially, amplitude reduction occurs distally in the nerves and only later in the disease is there some length-dependent reduction in amplitude as evidence that the intermediate segments have not been spared. The latter might be explained by a more general decrease of the blood-nerve barrier as reflected by increased protein leakage into the CSF (Arnason, 1984). This 'humoral' hypothesis further implies a proximal predilection of lesions (*see* fig. 8B). In this study we were only able to show that proximal conduction was slow on the basis of prolonged F responses. Electrical stimulation of spinal roots, a recently introduced technique, makes it feasible to test this part of the hypothesis directly and quantitatively (Mills and Murray, 1985; Young and Cracco, 1985).

The findings in Group A (fig. 8A) cannot be explained by a similar reasoning. In contrast to Group B, the motor fibres are relatively spared distally and more affected in the arm segment where the blood-nerve barrier is optimal under normal circumstances. In Group A patients, even more exciting is the finding that sensory fibres are spared where the adjacent motor fibres are maximally involved (Fig. 8A). At present there is no explanation for these findings, but the solution may be of importance for the understanding of the aetiology and the pathogenesis of the GBS.

## ACKNOWLEDGEMENTS

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# CHANGES IN PRESYNAPTIC INHIBITION OF Ia FIBRES IN MAN WHILE STANDING

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## SUMMARY

Presynaptic inhibition of homonymous Ia afferent terminals to soleus, quadriceps and tibialis anterior motoneurons and of heteronymous Ia fibres from quadriceps to soleus was compared in the same subjects when standing without support and during a control situation (sitting or standing with back support). Changes in presynaptic inhibition of Ia fibres were indirectly deduced from alterations in the amount of monosynaptic Ia facilitation elicited in motoneurons by a constant conditioning stimulation. Facilitation was measured during the first 0.5 ms when the monosynaptic Ia excitatory postsynaptic potential (EPSP) was not yet contaminated by polysynaptic effects evoked by the conditioning stimulation. Two indirect methods were used to provide an estimate of the size of the conditioning Ia EPSP: (1) the resulting H reflex facilitation; and (2) the peak of increased firing probability elicited in voluntarily activated motoneurons by stimulation of homonymous and heteronymous Ia fibres (poststimulus time histogram PSTH method). Only those PSTH experiments in which the 'spontaneous' firing rate of the motor unit was identical in the different positions, thus ensuring an identical net synaptic drive to the motoneuron, were considered. Under these conditions it is assumed that changes in the size of the peak of facilitation elicited by the monosynaptic Ia volley are likely to be caused by changes in presynaptic inhibition of Ia fibres.

It is argued that the substantial changes in monosynaptic Ia excitation observed when standing without support probably reflect changes in presynaptic inhibition of Ia fibres. Under this interpretation, presynaptic inhibition of Ia fibres to soleus motoneurons is increased while standing without support, whereas presynaptic inhibition of homonymous Ia fibres to quadriceps motoneurons is decreased. There is no evidence for a change in presynaptic inhibition of Ia fibres to tibialis anterior motoneurons. The resulting alterations in the gain of the monosynaptic reflex of these muscles are discussed in relation to the possible role of the monosynaptic stretch reflex in human gait.

## INTRODUCTION

The finding that in a steady state the gain of the stretch reflex is low (*see* Matthews, 1972; Vallbo, 1974) has led some physiologists to question the functional importance of the monosynaptic myotatic loop (Gottlieb and Agarwal, 1980; Allum, 1981). In fact, during a phasic movement this gain might be continuously changing according to the requirements of each movement (Rack, 1981). The first evidence for such a change in the gain of the stretch reflex in man was established by

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Newsom-Davis and Sears (1970) in their work on intercostal muscles during breathing movements. Presynaptic inhibition of Ia fibres is one of the spinal mechanisms which can alter the effectiveness of the monosynaptic stretch reflex. Thus at the onset of movement, decrease in presynaptic inhibition of Ia fibres projecting to voluntarily activated motoneurons contributes to stretch reflex enhancement (Hultborn *et al.*, 1987*b*).

Considerable changes in the effectiveness of the Ia-mediated spinal stretch reflex of the soleus muscle have been observed during various locomotor activities in man. It is large during running (Dietz *et al.*, 1979) where it probably contributes to load compensation (Noth and Dietz, 1979), whereas it is depressed at the onset of the stance phase of gait (Dietz *et al.*, 1984), which could depend on the increased presynaptic inhibition of Ia fibres as previously suggested by Morin *et al.* (1982). A depression of the soleus monosynaptic stretch reflex has also been found while standing without support (Elner *et al.*, 1976; Dietz *et al.*, 1984). The present investigation was undertaken to explore the amount of presynaptic inhibition on Ia fibres to various motor nuclei in freely standing man.

Changes in presynaptic inhibition of Ia fibres were indirectly deduced from changes in the monosynaptic Ia facilitation elicited on motoneurons by a constant conditioning stimulation. Two indirect methods were used to provide an estimate of the size of the conditioning Ia excitatory postsynaptic potential (EPSP): (1) measurement of the H reflex facilitation evoked by a heteronymous Ia volley, which has recently been proposed as a method to evaluate changes in presynaptic inhibition of Ia fibres (Hultborn *et al.*, 1987*a*); and (2) the poststimulus time histogram (PSTH) method which extracts from the naturally-occurring spike train only those changes in firing probability which are time-locked to the stimulation (Moore *et al.*, 1970; Stephens *et al.*, 1976; Kirkwood and Sears, 1978; Ashby and Zilm, 1982). Thus the increased firing probability of voluntarily activated motor units (in soleus, quadriceps and tibialis anterior) occurring at monosynaptic latency after stimulation of Ia fibres was compared in the control situation (standing with back support) and when standing without support. Only those experiments in which the 'spontaneous' firing rate of the motoneuron was identical in the different positions were considered. In such cases the net synaptic drive to the motoneuron may be considered as unchanged and an alteration in the size of the Ia-induced peak of facilitation is assumed to be caused by a change in presynaptic inhibition of Ia fibres (Ashby and Verrier, 1980).

Prominent changes in monosynaptic Ia facilitation of extensor motoneurons were observed while standing without support. Monosynaptic Ia facilitation of soleus motoneurons was decreased, whereas monosynaptic Ia facilitation of quadriceps motoneurons was increased. It is argued that these changes in the efficiency of Ia volleys to facilitate homonymous and heteronymous extensor motoneurons are caused by changes in presynaptic inhibition of Ia fibres. These findings are discussed in relation to the requirements of human gait.

## METHODS

### *General experimental procedure*

The experiments were carried out on 7 healthy subjects from the departmental staff aged 31–52 yrs, all of whom gave informed consent to the experimental procedure. In all the subjects the experiments were repeated many times to test the reproducibility of the results.

*Position.* The experiments were performed in three positions: sitting, standing with the back supported at shoulder level, standing without support. In the sitting position the examined leg was loosely fixed with the hip semiflexed (120°), the leg extended and the ankle at 100° While standing, with or without support, the explored leg was placed forward, the hip being slightly flexed (160°–170°), the knee fully extended and the ankle at 100°–110°. The subjects were asked to put all their body weight on the unexplored leg. Thus, even while standing without support, they were able to maintain the position without any contraction from the quadriceps, the soleus or the tibialis anterior, except for the 'single motor unit activity' required to construct the PSTH (*see* below). This absence of muscular activity was verified throughout the experiments by electromyographic (EMG) recording

*Stimulation and recording.* Surface electrodes were used both for stimulation and recording Rectangular current pulses of 0 5 ms duration delivered by standard constant current stimulators were used for stimulation. Stimulation was applied through a unipolar electrode, the active electrode being placed in the femoral triangle to stimulate the femoral nerve and in the popliteal fossa to stimulate the tibial nerve, or through a pair of electrodes (1.5 $cm^2$ silver plates) placed 2 cm apart at the level of the head of the fibula to stimulate the common peroneal nerve. The stimulus current delivered by the stimulators was measured by a current probe (Tektronix 6021) Since it is very difficult to record incoming volleys in man, the stimulus intensity has been expressed in multiples of the threshold intensity for the motor M wave (× motor threshold, MT). The surface EMG was recorded from pairs of nonpolarizable disc (0.9 cm diameter) electrodes placed over the bellies of vastus lateralis (20–25 cm above the patella), vastus-crureus (6–8 cm above the patella), soleus (below the gastrocnemius muscles) and tibialis anterior (8–12 cm below the patella).

### *Facilitation of the soleus H reflex by a heteronymous Ia volley from quadriceps*

The soleus H reflex, evoked by stimulation of the tibial nerve, was measured in terms of the amplitude of the compound muscle action potential. The reflex responses were analysed by computer 'on line' and the results stored on disc for further analysis.

Heteronymous Ia facilitation of the soleus H reflex was obtained by stimulating the femoral nerve with a constant intensity (either 1.2 × MT or an intensity supramaximal for the maximum M wave in the quadriceps muscle). The first 0.5 ms of this heteronymous Ia facilitation from quadriceps to soleus has been demonstrated to be monosynaptic and uncontaminated by any polysynaptic effect (Hultborn *et al.*, 1987*a*) Thus we first established the earliest conditioning-test interval at which it was possible to elicit this facilitation, using steps of 0.1 ms; the interval then chosen was 0.2–0.4 ms longer. Under these conditions the reflex facilitation depends only on the size of the monosynaptic conditioning EPSP A constant conditioning stimulation should elicit an EPSP of constant size in the motoneurons, and thus a constant amount of reflex facilitation, unless the amount of presynaptic inhibition of Ia fibres is changing; a decrease in the facilitation may be ascribed to an increase in presynaptic inhibition of the heteronymous Ia fibres from quadriceps to soleus.

The susceptibility of an H reflex to facilitation (and inhibition) varies with the size of the reference (unconditioned) reflex. At low reflex amplitudes (below 10–15% of the maximum M wave amplitude), the susceptibility of the H reflex to facilitation and inhibition increases with the increase in size of the unconditioned reflex (for references, *see* Hultborn *et al.*, 1987*a*). Since in the standing position the soleus H reflex is often depressed (*see* fig 8A), the test stimulus intensity was adjusted (i.e., increased) so that the reference (unconditioned) H reflex attained the same size as in the control situation (sitting or standing with support)

Sequences in the control situation and while standing without support were alternated. Twenty unconditioned and 20 conditioned reflexes were presented randomly in each sequence. To ensure the reproducibility of the results, at least 5 sequences were repeated using the same stimulation parameters. The statistical significance of the results was examined by an F test.

### *Assessment of the increased firing probability occurring at monosynaptic latency in single voluntarily activated motor units*

PSTHs of voluntarily activated motor units in soleus, quadriceps and tibialis anterior muscles were constructed for the period following stimulation of the homonymous nerve. PSTHs in soleus motor units were also constructed after stimulation of the heteronymous femoral nerve. Stimulation of homonymous (and heteronymous from quadriceps to soleus) low threshold afferents has been shown to evoke an early peak of increased firing probability (whose latency is the same as that of the corresponding H reflex) which has been attributed to monosynaptic connections of muscle spindle Ia afferents (Mao *et al*, 1984; Hultborn *et al.*, 1987*a*). The amplitude of this peak was used to provide an estimate of the size of the monosynaptic EPSP elicited by stimulation of homonymous (or heteronymous from quadriceps to soleus) Ia fibres in various positions

Stimulation of the tibial, femoral and common peroneal nerves, as described above, was always set to be subthreshold for the compound H reflex of the voluntarily activated muscle. The EMG from soleus, quadriceps (vastus lateralis) and tibialis anterior was recorded with surface electrodes while the subjects performed a very weak and steady contraction of the corresponding muscle. After some training, it was always possible to isolate an individual motor unit either because it was the only one active or because it was significantly larger than the others. In all experiments, the strength of the voluntary contraction was very weak (well below 5% of the maximal voluntary contraction), the motor units studied being, therefore, all low-threshold units. The EMG potentials of single motor units were converted into standard pulses by a discriminator with a variable trigger level. The motor unit potential and the trigger pulse were continuously monitored to detect false triggers due to other motor units and to ensure that motor unit shape and size as well as trigger position remained constant within and between sequences. Special care was taken to ensure that the same motor unit was recorded in the different positions, which was achieved by asking the subject to continue the contraction while passing from one position to another. This was impossible when passing from sitting to standing, but most subjects were, after some training, able to keep the same unit firing when passing from standing with back support to standing without support. The stimulation of the nerves was triggered at a fixed delay (D) after the preceding motor unit discharge (Fournier *et al*, 1986) and the latency of the following motor unit potential was computed. The PSTH of the voluntarily activated motor unit discharge was constructed for the period 20 to 60 (or 50) ms following the stimulation, using 0.5 ms bins When the nerve stimulation is delivered at a fixed interval after the previous discharge, it is possible to choose a delay when the probability for a new discharge is high (with the relatively regular firing frequency during voluntary contraction) This implies that the number of stimulations necessary to reveal obvious peaks in the PSTH can be much lower than if nerve stimulations are given without fixed reference to the previous motor unit discharge. This was especially important because the *same* motor unit had to be tested in different positions. Stimulation at a fixed interval after the previous discharge also implies that the probability of discharge in the PSTH does not depend only on the postsynaptic potentials evoked by the stimulation, but also on the motoneuron membrane trajectory during the interspike interval. To take account of the latter, a histogram of firing probability was also constructed in a control situation without stimulation and compared with the histogram obtained with nerve stimulation. Situations with and without stimulation were randomly alternated (same number of triggers) within a sequence, the equivalent bins in both histograms being obtained at the same moment of the motoneuron membrane trajectory.

A $\chi^2$ test was used to determine whether in each bin the firing probability following stimulation differed in the two positions studied (standing with and without support).

## RESULTS

### *Changes in the amount of heteronymous Ia facilitation of the soleus H reflex*

Stimulating the femoral nerve results in a facilitation of the soleus H reflex (*see* Hultborn *et al.*, 1987*a*). The early part of this facilitation, obtained with two different intensities of conditioning stimulation (1.2 × MT, ○; intensity supramaximal for the maximum M wave in the quadriceps, ●), is shown in fig. 1B. In this subject, facilitation of the test reflex started when the conditioning-test interval was −5.6 ms (if the afferent volleys following conditioning and test stimuli are to arrive at the spinal cord simultaneously, the test shock has to be delivered before the conditioning shock owing to the more proximal position of the conditioning electrode; in such cases the conditioning-test interval is said to be negative). A −5.4 ms stimulus interval (arrow in fig. 1B) was then chosen to obtain sizeable facilitation yet still ensure that the monosynaptic Ia EPSP in soleus motoneurons was not contaminated by any oligosynaptic (e.g., Ib) or polysynaptic effect. Under these conditions it has been shown that changes in reflex facilitation elicited by a

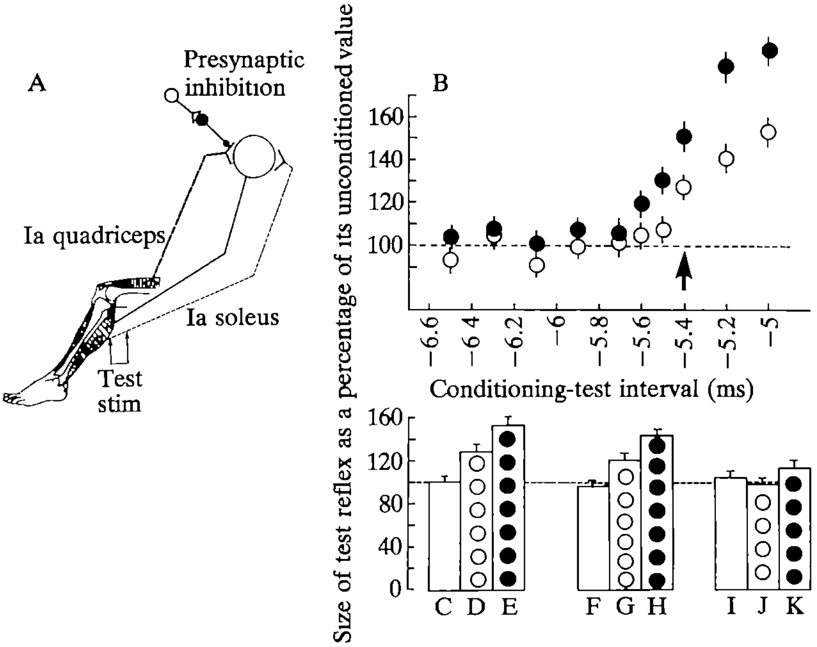

Fig. 1. Changes in heteronymous Ia facilitation from quadriceps to soleus while standing without support. A, schematic diagram of the experimental paradigm, the soleus H reflex is conditioned by a heteronymous Ia volley from quadriceps, whose efficiency to facilitate the reflex depends on presynaptic inhibition, bars and the small filled circle indicate excitatory and inhibitory synapses, respectively. B, time course of the early heteronymous Ia facilitation with two different intensities of conditioning stimulation (1.2 × MT, ○, supramaximal for maximum M, ●); the arrow indicates the conditioning-test interval used in C–K. C–K, each column represents an average of 100 trials where the size of the reflex is expressed as a percentage of its reference value in the sitting position. Vertical bars = 1 SEM. Trials illustrating the size of the reference reflex (C, F, I) and the reflex facilitated by 1.2 × MT (D, G, J) and supramaximal (E, H, K) femoral nerve stimulation are shown for the three situations: sitting (C–E), standing with support (F–H) and standing without support (I–K).

constant conditioning volley faithfully reflect changes in the amount of vibration-induced presynaptic inhibition on Ia fibres: the smaller the facilitation, the stronger the presynaptic inhibition (Hultborn *et al.*, 1987*a*).

It is of course essential that the conditioning stimulation to the femoral nerve elicits the same Ia afferent volley in the different positions. In all subjects the intensity of the conditioning stimulation was therefore adjusted (1.2 × MT) so that it evoked a small M wave in the quadriceps muscle, and the stability of the conditions of stimulation was inferred from the constancy of this M wave. It could be argued, however, that a constant stimulation of $\alpha$-motor fibres does not necessarily imply a constant stimulation of Ia afferents. For this purpose a much stronger conditioning stimulation (twice the intensity required to obtain the maximum M wave in the quadriceps muscle) was also used. It is certain, therefore, that in the 5 subjects who were able to maintain the required standing position, despite such stimulation, all quadriceps Ia fibres were activated by this largely supramaximal stimulation, whatever the position.

A typical example of the central finding of the present experiments, i.e. that heteronymous Ia facilitation to soleus motoneurons is decreased while standing without support, is illustrated in fig. 1C–K. Averages of 100 trials show the size of the reference and facilitated reflexes in the three positions. The size of the reference H reflex in the sitting position (which was 29% of maximum M) was set as 100% (fig. 1C). Femoral nerve stimulation evoked a significant facilitation of the reflex in this position: 128% with the 1.2 × MT conditioning stimulation (fig. 1D) and 158% with the supramaximal stimulation (fig. 1E). Fig. 1F–H, shows that this facilitation was not significantly changed when standing with back support. When standing without support, the reference H reflex size was decreased (a decrease which reduced the test reflex by no more than 50% of its control value), and it was necessary to increase the test stimulus intensity to restore the reference reflex size to its value in the sitting position (fig. 1I). Under these conditions there was a marked decrease in the facilitation evoked by the supramaximal stimulation (fig. 1K) and a complete disappearance of the facilitation evoked by the 1.2 × MT conditioning stimulation (fig. 1J). Similar results, always highly significant ($P<0.01$), were found in all subjects explored in this way.

The effect of standing position on heteronymous Ia facilitation of the soleus H reflex was explored while reference H reflexes of *different size* (results obtained in the same session) were conditioned by supramaximal stimulation of the femoral nerve (fig. 2). In the sitting position, reflex facilitation became smaller when the amplitude of the reference reflex was increased (as already shown; *see* Meinck, 1980). When standing without support, the facilitation induced by stimulation of the femoral nerve was markedly decreased, whatever the size of the reference reflex. Thus the decreased facilitation observed while standing without support can be obtained with large test reflexes, recruiting high threshold motor units, as well as with small reflexes which recruit the lowest threshold motoneurons (*see* Burke, 1981).

It has been shown in a previous paper that such a decrease in heteronymous Ia

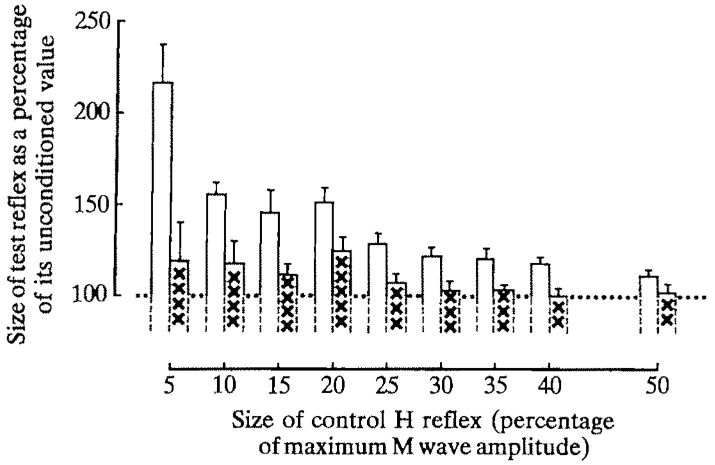

FIG 2. Comparison of heteronymous Ia facilitation of soleus H reflexes of different sizes when sitting (open columns) and standing without support (columns with crosses) Same experimental paradigm as in fig 1 Conditioning stimulation to the femoral nerve was supramaximal for the maximum M wave in quadriceps The facilitated H reflex (expressed as a percentage of its unconditioned value) is plotted against the control reflex size (expressed as a percentage of the maximum motor M wave amplitude) Each column represents the mean of 20 measurements Vertical bars = 1 SEM

facilitation is likely to reflect an increase in presynaptic inhibition of Ia fibres from quadriceps to soleus (Hultborn *et al.*, 1987*a*). An alternative explanation would be that in the standing position (e.g., because of a change in the vestibular input to motoneurons) there could be a widening of the 'usual' threshold range within the motoneuron pool resulting in a decrease in the slope of the input-output relation of the monosynaptic reflex (*see* Discussion). With such a change within the pool, a constant conditioning excitatory input to motoneurons could recruit fewer neurons, thus producing a smaller reflex facilitation than in the control situation. To exclude this possibility EPSPs were also assessed in individual motoneurons.

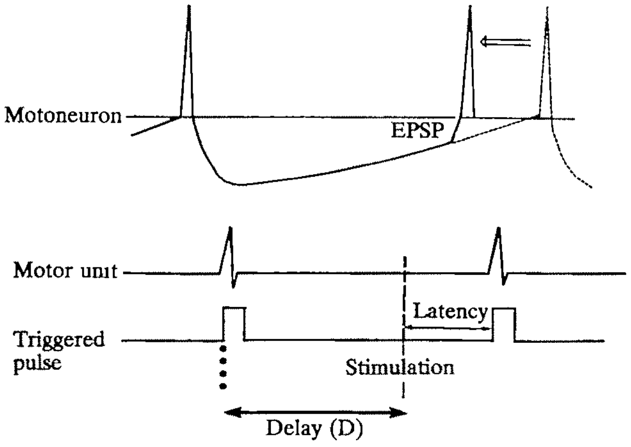

FIG. 3. Schematic diagram illustrating the experimental design to construct PSTHs, the stimulation being triggered at a fixed delay (D) after the previous spike. *Upper row*, motoneuron discharges and the motoneuron membrane trajectory during the interspike interval Interrupted spike = 'spontaneous firing', double arrow aiming at continuous spike = a stimulation-induced EPSP advances the spike Corresponding motor unit potentials (*second row*) are converted into standard pulses (*third row*) and the latency of the first spike following stimulation is computed to construct the PSTH

### *Changes in the Ia-induced increase in firing probability of voluntarily activated motor units*

The experimental design is illustrated in fig. 3. In the present experiments, stimulation was triggered at a fixed delay D after the previous spike (*see* Methods) and the latency of the first spike following stimulation was computed to construct the PSTH. A stimulation-induced EPSP which causes the motoneuron to discharge produces an increase in firing probability at a latency which is the sum of the peripheral afferent and efferent times plus the central latency of the effect. It has been shown in the cat that the profile of increased firing probability in the PSTH is a combination of the first derivative of the underlying EPSP and of the EPSP itself (Kirkwood and Sears, 1982*b*), the weight of the derivative being smaller when the EPSP is small with respect to the synaptic noise (Gustafsson and McCrea, 1984). The amplitude of the peak in the PSTH also depends on the synaptic drive responsible for the repetitive motoneuron firing (Ashby and Zilm, 1982). With the method used here (stimulation triggered at a fixed delay after the previous spike), increasing motoneuron firing frequency results in an increase in the peak of facilitation. Because of the increased synaptic drive necessary to make the motoneuron discharge more rapidly, a given EPSP evoked at a given delay after the previous spike can more easily overcome the postspike afterhyperpolarization.

*Reduction of the heteronymous Ia facilitation from quadriceps to soleus motoneurons when standing without support.* Fig. 4 shows the results obtained from a soleus motor unit, which had a very low firing rate (5 pulses/s). The delay (D)

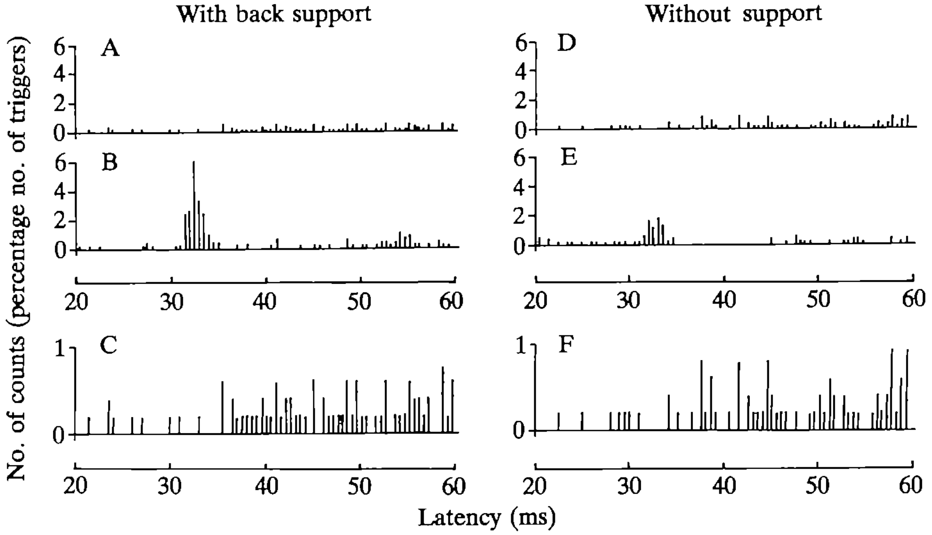

FIG. 4. Time histograms of the discharge of a soleus voluntarily-activated motor unit after stimulation (supramaximal for α-motor fibres) of the femoral nerve while standing with (A–C) or without (D–F) support. Histograms obtained without nerve stimulation are shown in A and D, and in C and F (with an expanded scale of the ordinate). PSTHs obtained after nerve stimulation are shown in B and E. Note that the spontaneous firing interval was very similar in the two positions. 205.3 (+10.3) and 205.8 (+10.6) ms. Delay (D) between the previous spike and the stimulation was 120 ms. Number of triggers used for each histogram was 400

between the previous spike and the trigger was 120 ms. Results obtained while standing with (fig. 4A–C) and without (fig. 4D–F) support are compared. In each position the PSTHs constructed after femoral nerve stimulation (fig. 4B, E) were compared with histograms obtained in the control situation without stimulation (figs. 4A, D).

The background firing probability observed without stimulation, which reflects the motoneuron membrane trajectory during the interpsike interval, is better displayed in figs. 4C and F (that show the same results as in figs. 4A and D but with an expanded ordinate scale). The spontaneous firing progressively increased with increasing time intervals and reached a maximum about 200 ms after the previous spike, i.e. 80 ms (200 − 120) after the trigger (an interval which is not represented in fig. 4).

Here too the stimulus applied to the femoral nerve was largely supramaximal for the maximum M wave in the quadriceps to ascertain that all Ia fibres were stimulated in both positions. When standing with back support, femoral nerve stimulation elicited an increase in firing probability with a latency of 31.5 ms (fig. 4B). Experimental evidence has been given that this facilitation is Ia in origin (Hultborn *et al.*, 1987*a*). This peak of heteronymous Ia facilitation was significantly smaller than that caused by stimulation of homonymous Ia fibres (compare the scale of the ordinate in fig. 4B and 5B). The effect of this supramaximal stimulation of the femoral nerve was then assessed while standing without support. The Ia-induced increase in firing probability was significantly reduced ($P < 0.001$) with respect to standing with back support (compare fig. 4E and B).

As seen above, the amplitude of the peak of facilitation depends not only on the underlying EPSP (a combination of its peak amplitude and first derivative) but also on the firing rate of the motoneuron. The subjects were therefore asked to keep the firing rate as similar as possible in the two positions and only experiments in which this attempt was successful were retained for further analysis. Three criteria concerning the data obtained without nerve stimulation were used as a basis for similarity: the mean interspike interval (m), its standard deviation (SD) and the total number of counts (n) within the window of analysis. In the experiments illustrated in fig. 4 these three factors were almost identical in the two situations: mean (205.3 and 205.8 ms), SD (10.3 and 10.6 ms), n (77 and 76). The distribution of spikes within the analysis window was also very similar (*see* fig. 4C, F). Under these conditions it has been suggested that the decrease in the Ia-induced peak in the PSTH reflects a decrease in the underlying Ia EPSP (Ashby and Verrier, 1980).

This decrease in the Ia EPSP elicited by stimulation of the femoral nerve can be taken as a sign of increased presynaptic inhibition on the corresponding Ia fibres only if the Ia facilitation is exclusively mediated through a monosynaptic pathway. Even though quadriceps Ia fibres have monosynaptic projections onto soleus motoneurons (Hultborn *et al.*, 1987*a*), it is possible that oligosynaptic group I excitatory pathways described in the cat (Jankowska *et al.*, 1981; Kirkwood and Sears, 1982*a*) also contribute to the Ia-induced peak (Burke *et al.*, 1984). However, during its earliest part (first 0.5 ms bin) the monosynaptic Ia EPSP is not yet contaminated by any oligosynaptic effect (Hultborn *et al.*, 1987*a*). It is therefore of extreme importance that the first bin of the peak of increased firing probability was decreased when standing without support (fig. 4E). This strongly suggests a decrease in the monosynaptic heteronymous Ia EPSP and thus an increase in presynaptic inhibition of Ia fibres from quadriceps to soleus motoneurons (*see* Discussion).

Only 3 subjects were able to hold the same unit despite such strong stimulation, and 7 units were recorded during a time long enough to construct the 4 different histograms (A, B, D, E) with 400 triggers for each. However, only in 3 cases (1 in each subject) was it possible to obtain an identical firing rate in the two positions. In these 3 cases the peak of heteronymous Ia facilitation, and in particular its first bin, was significantly reduced ($P < 0.01$ or $< 0.001$) when standing without support.

*Reduction of the homonymous Ia facilitation of soleus motoneurons when standing without support.* Fig. 5, which is arranged like fig. 4, shows the results from a soleus motor unit (mean interspike interval (ISI) 155 ms; delay (D) 110 ms) conditioned by stimulation of the tibial nerve (0.83 × MT). When standing with support this stimulation elicited an increase in firing probability with a latency similar to that of the soleus H reflex (fig. 5B). This peak was lodged within four consecutive bins which fits the mean duration found by Mao *et al.* (1984) and Burke *et al.* (1984). This early peak has been attributed to monosynaptic connections of muscle spindle Ia afferents (Mao *et al.*, 1984), although a contribution of oligosynaptic group I excitatory pathways to the early EPSP appears possible (Burke *et al.*, 1984). As discussed above, however, in its first 0.5 ms bin, the facilitation is only produced by the monosynaptic Ia EPSP.

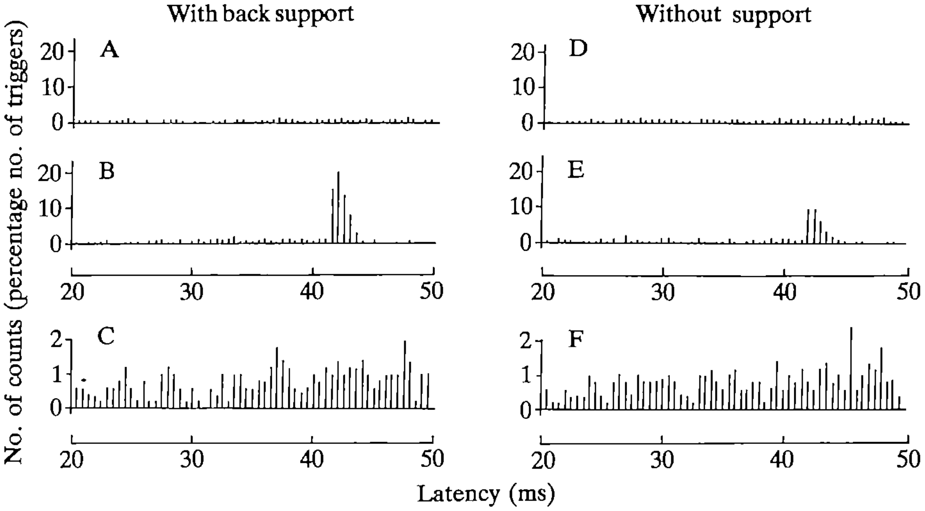

FIG. 5. Time histograms of the discharge of a soleus voluntarily-activated motor unit after homonymous stimulation (0.83 × MT) of the tibial nerve A–F, same legend as in fig. 4. Spontaneous firing interval in the two positions 154.7 (+8.2) and 155.6 (+8.2) ms. Delay (D) 110 ms. Number of triggers, 500.

The size of the EPSP, and thus the amplitude of the peak, increases along with the intensity of the nerve stimulation (Mao *et al.*, 1984; Fournier *et al.*, 1986). However, when the probability of firing is high, it can no longer increase significantly with the intensity. In such a case, it is possible that a change in the size of the Ia EPSP does not produce any significant change in the peak of facilitation. The intensity of the stimulation (here 0.83 × MT) was therefore carefully adjusted to produce a sizeable facilitation yet still ensure that an increase in the intensity enhanced the peak in the PSTH.

When standing without support, the intensity of the tibial nerve stimulation was also adjusted to 0.83 × MT. If the intensity was the same multiple of the M threshold, it could be assumed that tibial nerve stimulation elicited a similar Ia afferent volley in the two positions (in some cases it was even possible to elicit the M threshold with the same intensity of stimulation in the two positions). The Ia-induced increase in firing probability was significantly smaller ($P<0.001$) than when standing with support (compare fig. 5E and B). Here also the mean firing rate (154.7 and 155.6 ms), its SD (8.2 ms), the number of counts (238 and 237) and the distribution of spikes within the window of analysis (fig. 5C and F) were almost identical in the two positions.

Fifteen units (from 4 subjects) were so recorded. However, only 5 recordings (from 4 subjects) were satisfactory, that is, with an identical firing rate in the two positions. In all these 5 units the Ia-induced increase in firing probability was significantly ($P<0.01$) reduced in its earliest part when standing without support.

*Increase in the homonymous Ia facilitation to quadriceps motoneurons when standing without support.* Fig. 6 deals with the changes in firing probability of a quadriceps

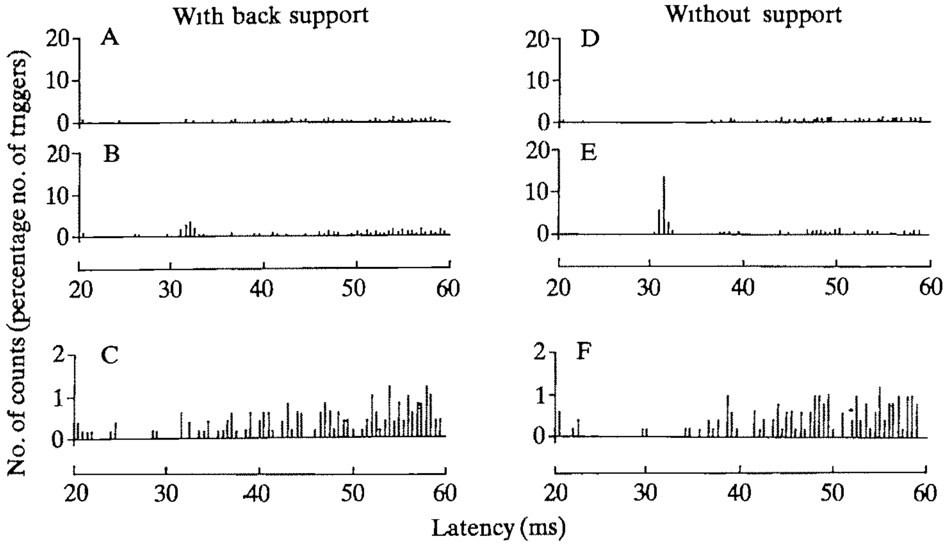

FIG. 6. Time histograms of the discharge of a quadriceps voluntarily-activated motor unit after homonymous stimulation (0 7 × MT) of the femoral nerve A–F, same legend as in fig 4 Spontaneous firing interval in the two positions 111 6 (+10.2) and 112 8 (+9 2) ms Delay (D), 55 ms Number of triggers, 500.

(vastus lateralis) motor unit when conditioned by a weak (0.7 × MT) stimulation of the femoral nerve. The mean 'spontaneous' firing interval was 112 ms and the delay (D) 55 ms. When standing with back support this femoral nerve stimulation elicited a small peak of facilitation (fig. 6B), whose latency (31 ms) was the same as that of the quadriceps H reflex. This early peak has been attributed to a monosynaptic Ia EPSP (Mao *et al.*, 1984; Fournier *et al.*, 1986) Even though a possible oligosynaptic contribution to the EPSP has to be considered, here too it can be ascertained that the first bin of this facilitation is produced by a monosynaptic Ia EPSP.

When standing without support the Ia-induced increase in firing probability was markedly enhanced ($P < 0.001$), an enhancement which was also significant in the first bin (fig. 6E). Here again the mean firing rate (ISI 111.6 and 112.8 ms), its SD (10.2 and 9.2 ms), the number of counts (132 and 128) and the distribution of spikes within the window of analysis (figs 6C, F) were almost identical in the two positions. Fourteen motor units from 6 subjects were so recorded. Nine units (from 5 subjects) had an identical firing rate in the two positions and were retained for further analysis. In all these 9 units the Ia-induced increase in firing probability was significantly enhanced ($P < 0.01$) in its earliest part when standing without support. This increased efficiency of the Ia volley to facilitate quadriceps motoneurons suggests a decrease in presynaptic inhibition of homonymous quadriceps Ia fibres.

The number of Ia fibres activated by the stimulation could be assumed to be the same in the two positions, since, in both cases, the intensity of stimulation was adjusted to be the same multiple (here 0.7 × MT) of the M threshold. Furthermore,

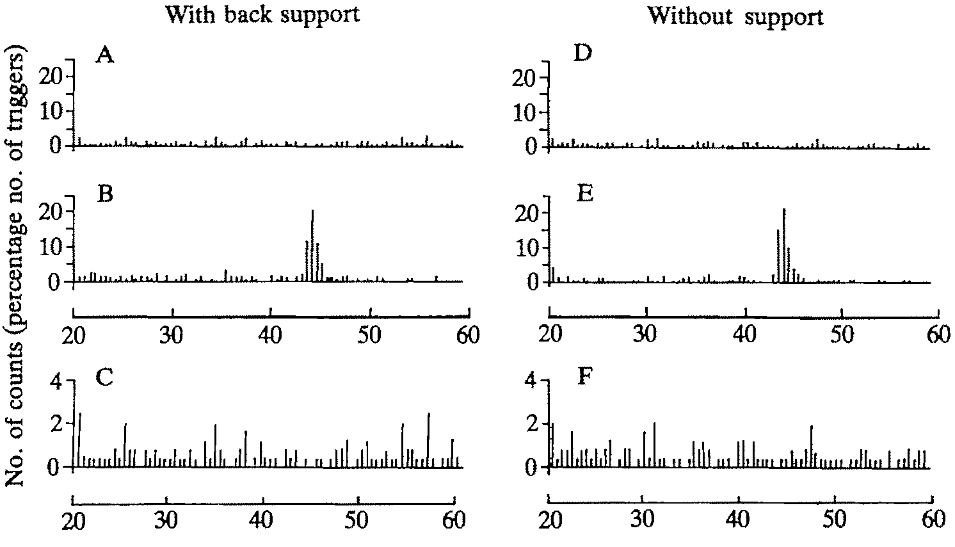

FIG 7. Time histograms of the discharge of a tibialis anterior voluntarily activated motor unit after homonymous stimulation (1 × MT) of the common peroneal nerve. A–F, same legend as in fig. 4. Spontaneous firing interval, in the two positions: 109.3 (+12.3) and 108.2 (+12.1) ms. Delay (D), 70 ms. Number of triggers, 250.

opposite results obtained in soleus and quadriceps motor units (results obtained in the same session with the same 0.7 × MT femoral nerve stimulation) strongly argue against possible changes in the number of Ia fibres activated by the stimulation being an important factor: in soleus motoneurons the peak following femoral nerve stimulation was reduced in the standing position when using a weak (0.7 × MT) as well as a strong (fig. 4) stimulus. Under these conditions the opposite effect of standing position on quadriceps (increased peak) and soleus (decreased peak) motoneurons cannot be explained by a change in the number of Ia fibres activated by the stimulus applied to the femoral nerve.

*Absence of alteration in the homonymous Ia facilitation of tibialis anterior motoneurons while standing without support.* Stimulation of the common peroneal nerve (1 × MT) evokes an early peak of facilitation in the PSTH of voluntarily activated tibialis anterior motor units (fig. 7), which has also been attributed to a monosynaptic Ia EPSP (Ashby and Zilm, 1982). Eleven motor units (from 6 subjects) had an identical firing rate when standing with or without support. In all cases, as shown in fig. 7 ('spontaneous' firing interval 109 ms, delay (D) 70 ms), the peak of increased firing probability (and in particular its first bin) had the same order of magnitude in the two positions (fig. 7B, E).

### *Changes in the amplitude of the soleus and quadriceps H reflexes when standing without support*

At a given intensity of stimulation the amplitude of the H reflex depends on both the motoneuron excitability and the amount of presynaptic inhibition on the Ia fibres mediating the afferent test volley. The marked changes in the efficiency of a monosynaptic Ia volley to facilitate homonymous motoneurons (fig. 5, 6), which are assumed to reflect changes in presynaptic inhibition of Ia fibres (*see* Discussion), were therefore expected to produce corresponding alterations in the amplitude of

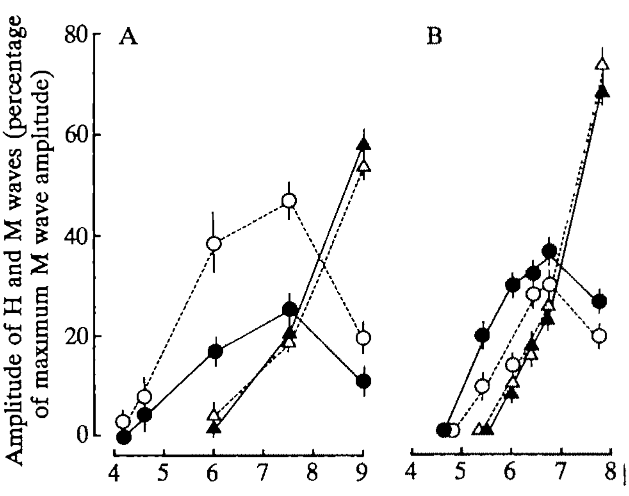

FIG 8. Recruitment curves of the soleus (A) and quadriceps (B) H reflexes while standing with (open symbols) or without (filled symbols) support. The amplitudes of the H reflex (circles) and of the direct motor M wave (triangles), expressed as a percentage of the amplitude of the maximum M wave, are plotted against the intensity of the test stimulus applied to the tibial nerve (A) or the femoral nerve (B).

the soleus and quadriceps H reflexes while standing without support. Fig. 8 shows the variations of the amplitude of the H wave and of the direct motor M wave with the test stimulus intensity while standing with and without support. The stability of the conditions of stimulation when the position changes was inferred from the constancy of the M wave, and the recruitment curves of the H reflex obtained in each position were compared only when the corresponding curves of the M wave could be superimposed (*see* fig. 8A, B). This was achieved in 6 subjects for the soleus and in 5 subjects for the quadriceps. A significant decrease in the amplitude of the soleus H reflex was observed in 4 subjects while standing without support (the largest inhibition is illustrated in fig. 8A) but in the 2 others, although seen, it was not statistically significant. An increase in the amplitude of the quadriceps H reflex was, on the contrary, observed during stance without support in 4 subjects, no changes being observed in the remaining subject (in whom the amplitude of the soleus H reflex was not significantly modified either). It must be pointed out that in the 2 subjects who did not exhibit a significant modification of H reflex amplitude while standing without support, a clear change in the Ia-induced peak of facilitation was seen with the PSTH method. This discrepancy could be explained if the changes in presynaptic inhibition of Ia fibres were to be compensated by opposite postsynaptic events (e.g., an increased postsynaptic inhibition could mask a decreased presynaptic inhibition of Ia fibres). At any rate, even though H reflex amplitude does not only reflect the amount of presynaptic inhibition on Ia fibres, it is interesting to note that, in 4 subjects, inverse changes in the amplitude of the soleus and quadriceps H reflexes were observed.

## DISCUSSION

### *Evidence for changes in presynaptic inhibition of Ia fibres while standing without support*

In animal experiments the most direct evidence of presynaptic inhibition of Ia fibres is the depression of the monosynaptic EPSP evoked in motoneurons by a constant stimulation of Ia fibres and occurring without any observable change in motoneuron potential and conductance (Frank and Fuortes, 1957). Such direct evidence is obviously impossible to obtain in man. Thus in the present series of experiments, changes in presynaptic inhibition of Ia fibres were indirectly deduced from alterations in the amount of monosynaptic Ia facilitation elicited in motoneurons by a constant conditioning stimulation. The monosynaptic Ia facilitation was assessed during its first 0.5 ms, when it is yet uncontaminated by any subsequent oligosynaptic or polysynaptic effect. Two methods were used to provide evidence for changes in monosynaptic Ia facilitation evoked by a given conditioning stimulation: measurement (1) of the resulting H reflex facilitation, and (2) of the peak of facilitation evoked in individual voluntarily activated motoneurons (the PSTH method). Significant changes in this monosynaptic Ia facilitation were observed while standing without support. Compared with the control situation (sitting or standing with a back support) facilitation of soleus motoneurons was decreased, whereas facilitation of those innervating quadriceps was increased. Alterations in presynaptic inhibition of Ia fibres to extensor motoneurons might account for these modifications of Ia facilitation. Other possible interpretations must, however, be considered.

In PSTH experiments the height of the peak increases in proportion to both the amplitude of the EPSP and the magnitude of its rising slope (Kirkwood and Sears, 1982*b*; Fetz and Gustafsson, 1983). It is therefore impossible with this method to provide an exact measurement of the size of the Ia-induced EPSP. However, qualitatively speaking, the larger the EPSP, the higher the peak.

The question also arises whether changes in the underlying Ia EPSP are the only possible cause of alterations in the amount of facilitation.

1. In PSTH experiments, the height of the peak evoked by a given EPSP also depends on factors modifying the background excitability of the motoneuron when the stimulation is evoked. (1) The moment when the EPSP is evoked within the motoneuron membrane trajectory is important, and the earlier the EPSP occurs during the afterhyperpolarization of the motoneuron, the smaller the height of the peak (Fournier *et al.*, 1986). (2) Possible changes in postsynaptic events related to active maintenance of posture, whatever their origin (descending or peripheral), must also be considered. If excitatory, they would raise the background excitability of the motoneuron, thus producing an increase in the peak evoked in the PSTH by a given stimulation-induced EPSP; if inhibitory, they would have the opposite effect. However, the subjects were asked to keep the firing rate as similar as possible in the two standing positions and only the experiments in which this attempt was successful were considered. In such cases postsynaptic events related to the active maintenance of posture must have been counteracted by alterations in the voluntarily produced synaptic drive to motoneurons. Furthermore, figs 4–7C and F show that in the retained experiments the 'spontaneous' firing had a similar distribution within the window of analysis. This also suggests that, when standing with and without support, the motoneurons exhibited a similar background excitability (afterhyperpolarization + net synaptic drive) when the stimulation-induced EPSP was evoked. Thus a change in the size of the Ia-induced EPSP seems to be the most probable explanation.

2. The reduced heteronymous facilitation of the soleus H reflex could reflect a decrease in the size of the monosynaptic heteronymous Ia EPSP (Hultborn *et al.*, 1987*a*). Here also, an alternative explanation must be considered. It is conceivable that the vestibulospinal input to motoneurons is changed while actively maintaining the standing position, and vestibulospinal EPSPs are known to have a distribution within the motoneuron pool which is different from that of Ia EPSPs (*see* Burke, 1981). This could produce a widening of the 'usual' threshold range within the motoneuron pool and thus contribute to the smaller reflex facilitation. Under this assumption, because of the resulting decrease in the slope of the input-output relation of the monosynaptic reflex, a constant conditioning Ia EPSP would fire

fewer motoneurons than in the control situation. It is therefore of importance that a similar decrease in heteronymous facilitation of soleus motoneurons was observed in individual units where this factor does not have to be considered. The finding that the depression of the Ia-induced facilitation had the same dramatic order of magnitude when measured in individual units (fig. 4) as in the motoneuron population (figs 1–2) strongly suggests that the latter is also due to a decrease in the size of the conditioning Ia EPSP.

The question finally arises whether postsynaptic inhibition could produce a decrease in the size of the conditioning Ia EPSP (for soleus motoneurons), given the increase in membrane conductance underlying the inhibitory postsynaptic potential (IPSP): increasing the test stimulus intensity in reflex experiments or the voluntarily produced excitatory synaptic drive to the motoneuron in PSTH experiments compensates for the changes in motoneuron membrane potential but not for the changes in conductance. In fact, the extent to which monosynaptic Ia EPSPs are modified by conditioning postsynaptic inhibition has been examined recently in animal experiments with intracellular recording from motoneurons (Hultborn *et al.*, 1987*a*). It was found that, as long as postsynaptic inhibition is not very large (i.e., reducing the amplitude of a monosynaptic test reflex by no more than 50% of its control value), the falling phase of the EPSP is reduced, but its peak remains unchanged (this apparent discrepancy being due to fundamental biophysical circumstances; *see* Hultborn *et al.*, 1987a). In any event, in the present series of experiments the inhibition, whatever its origin, remained 'relatively moderate', since while standing without support the amplitude of the soleus H reflex was reduced by no more than 50% of its control value. Furthermore, the conditioning Ia EPSP was tested during its first 0.5 ms both in reflex and PSTH experiments, that is, before the time of its peak: thus it can be ensured that changes in conductance underlying possible IPSPs in motoneurons are marginally responsible for the decrease in Ia-induced EPSPs observed in the present series of experiments.

To sum up, indirect techniques, based on the assessment of the monosynaptic Ia facilitation, were used to provide an estimate of the underlying EPSP. Even though with these techniques it is not possible to measure the size of the EPSP directly, evidence is presented that the dramatic changes in Ia facilitation observed while standing without support reflect alterations in presynaptic inhibition of Ia fibres.

### *Differential control of presynaptic inhibition of Ia fibres to soleus, quadriceps and tibialis anterior motoneurons*

Contrasting with the seemingly diffuse pattern of distribution of presynaptic inhibition on Ia fibres of all ipsilateral muscles found in the spinal cat (Eccles *et al.*, 1962), the present results show that, when standing without support, presynaptic inhibition is differently controlled on Ia fibres to soleus (increased), quadriceps (decreased) and tibialis anterior (unchanged) motoneurons. A differential control of presynaptic inhibition on Ia fibres to various motor nuclei has also been found at the onset of voluntary contraction where presynaptic inhibition of Ia fibres to motoneurons of the contracting muscle is selectively decreased (Hultborn *et al.*, 1987*b*). These differential controls (during contraction or while standing) indicate that presynaptic inhibition on Ia terminals to different motoneuron pools is mediated (at least in part) through different interneuronal pathways. The present experiments also show that presynaptic inhibition on heteronymous Ia fibres from quadriceps to soleus and on homonymous soleus Ia fibres is similarly changed when standing without support. This confirms (*see* Hultborn *et al.*, 1987*b*) that the control of presynaptic inhibition on *heteronymous* Ia fibres depends on their target motoneurons rather than on their muscle origin.

### *Descending or peripheral origin of the changes in presynaptic inhibition of Ia fibres when standing without support*

Animal experiments have shown that interneurons mediating presynaptic inhibition, hereafter referred to as 'presynaptic interneurons', are subject to excitatory and inhibitory control from many higher centres (*see* Baldissera *et al.*, 1981). In man, it has been argued that the decrease in presynaptic inhibition on Ia fibres to motoneurons of the contracting muscle at the onset of movement is supraspinal in origin (Hultborn *et al.*, 1987*b*). Changes in presynaptic inhibition of Ia fibres observed in the present experiments might also reflect a descending influence modifying the excitability of 'presynaptic interneurons'.

However, a peripheral origin must also be considered. (1) A contraction of ipsilateral proximal muscles (such as iliopsoas), where the EMG was not monitored, was possible and the resulting group I discharge could have activated 'presynaptic interneurons' (for references, *see* Matthews, 1972). (2) While standing without support, there were muscle contractions in the contralateral limb. The resulting groups II-III discharge could have activated 'presynaptic interneurons' of the contralateral limb, since after administration of DOPA such a discharge has been shown to evoke presynaptic inhibition of contralateral Ia fibres in the spinal cat (*see* Baldissera *et al.*, 1981). Such peripheral controls could explain the increase in presynaptic inhibition on Ia afferents to soleus motoneurons. However, owing to the diffuse distribution of presynaptic inhibition evoked by afferent volleys found in the spinal cat (Eccles *et al.*, 1962), such a peripheral control, by itself, should also produce an increase in presynaptic inhibition of Ia fibres to quadriceps and tibialis anterior motoneurons. The finding that presynaptic inhibition of Ia fibres to soleus, quadriceps and tibialis anterior motoneurons is differently controlled suggests the involvement of a descending control. From the present results, however, it is impossible to know how the contraction-induced afferent discharge and this descending control interact to produce the different changes in presynaptic inhibition observed on Ia fibres to various motor nuclei.

### *Functional implications*

The increase in presynaptic inhibition of homonymous Ia fibres to soleus motoneurons while standing without support (fig. 5) certainly contributes to the depression of the soleus monosynaptic reflex found in this position. This depression of the reflex amplitude, when compared with a control value (obtained while standing with support or sitting), has been observed whatever the method used to elicit the reflex: electrical stimulation evoking an H reflex (fig. 8A), tendon tap

(Elner *et al.*, 1976) or postural perturbation eliciting a stretch reflex (Elner *et al.*, 1976; Dietz *et al.*, 1984). Accordingly, the soleus monosynaptic pathway was shown not to be significantly involved in the compensatory reactions following perturbation of the ankle position in freely standing man (Gurfinkel *et al.*, 1976).

This led to an interpretation of the reduction of the effectiveness of monosynaptic Ia excitation to soleus motoneurons while standing without support in terms of postural regulation: it was argued that a too strong monosynaptic stretch reflex could functionally destabilize posture (*see* Dietz, 1986), and that it would be disadvantageous to use the monosynaptic pathway to achieve postural reactions since the afferent volley and the 'central program of standing' could not interact at interneuronal level (Elner *et al.*, 1976). However, this should also apply to the quadriceps where, on the contrary, a decrease in presynaptic inhibition of homonymous Ia fibres was observed together with an increased monosynaptic reflex amplitude (fig. 8B).

An alternative explanation would be to assume that there could be a presetting of 'presynaptic interneurons' while standing without support so as to provide reflex action which might assist bipedal gait, since the soleus and quadriceps monosynaptic reflexes are differently modulated during the early part of the stance phase of gait. As compared with stance without support, the monosynaptic stretch reflex of the quadriceps is not modified (Dietz *et al.*, 1986), whereas the soleus monosynaptic reflex is markedly depressed (Dietz *et al.*, 1984; Capaday and Stein, 1986; Crenna and Frigo, 1987). A prerequisite for this interpretation is for the decrease in the soleus monosynaptic reflex during gait to be caused by an increased presynaptic inhibition of soleus Ia fibres. This has been suggested because, at an identical level of EMG activity, the H reflex is always smaller during walking than during steadily maintained contraction while standing (Morin *et al.*, 1982). This presynaptic interpretation has recently been supported by extensive modelling studies (Capaday and Stein, 1987*a, b*).

Opposite alterations in the effectiveness of Ia excitation to soleus and quadriceps motoneurons observed while standing without support and due to changes in presynaptic inhibition of Ia fibres are discussed hereafter with respect to the different role played by these two extensors during the stance phase of plantigrade gait. The gastrocnemius-soleus tension resists and restrains the ankle dorsiflexion produced by the resultant of the extrinsic forces (Sutherland *et al.*, 1980), but it is imperative that gastrocnemius-soleus tension be overcome by this resultant if the body is to be brought forward. An excessive soleus stretch reflex must therefore be prevented, for which increased presynaptic inhibition of soleus Ia fibres would be required. The role of the quadriceps contraction is quite different since in early stance, at the moment of the yield of the knee, it supports all the body weight. The increase in Ia excitation resulting from the decreased presynaptic inhibition of quadriceps Ia fibres may give a high safety factor to the quadriceps contraction, which could be of importance when walking on uneven ground. Lastly, the finding that presynaptic inhibition of tibialis anterior Ia fibres is unchanged while standing does not contradict this 'locomotor interpretation'. During walking, tibialis anterior contractions raise the foot and stabilize the ankle but, contrary to extensor muscles, they do not have to support the body weight or to resist the extrinsic forces.

There are, interestingly, other spinal mechanisms in man where the organization of the group I spinal pathways in the lower limb differs from that in the cat hindlimb, tending to increase the quadriceps stretch reflex and to decrease the soleus stretch reflex during gait: (1) presence of heteronymous Ia excitatory projections from soleus to quadriceps motoneurons and absence of Ia excitation from medial gastrocnemius to soleus motoneurons (Pierrot-Deseilligny *et al.*, 1981*b*); (2) depression of Ib inhibition to quadriceps motoneurons (but not to soleus motoneurons) by cutaneous afferents from the foot sole (Pierrot-Deseilligny *et al.*, 1981*a*).

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# KINEMATIC ANALYSIS OF MULTIPLE MOVEMENT COORDINATION DURING SPEECH IN STUTTERERS

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## SUMMARY

This study addresses the long-standing claim that stuttering reflects an impairment in the neuromotor coordination of multiple speech movements. Upper lip (UL), lower lip (LL), and jaw (J) kinematics for nonstuttered speech behaviours in stutterers and normal speakers were examined using quantitative indices of normal multiple movement coordination reported in recent studies of gait, reaching, grasping, and speech. While two measures of coordination – dynamic movement composition and intermovement motor equivalence – did not distinguish between stutterers and normals, stutterers manifested striking differences from normal on a third measure, the sequencing of UL, LL, and J movement onsets and velocity peaks. These findings suggest that, contrary to previous hypotheses, stutterers do not manifest general problems of coordination of speech movement. Instead, stuttering appears to be associated with a specific impairment in multiple movement coordination associated with sequencing of those movements.

## INTRODUCTION

Perhaps one of the most widely accepted hypotheses concerning the speech disorder of stuttering is that this is an impairment in coordination of speech movements. For over 50 years experiments on stuttering have focused on 'dyscoordination' associated with *instances of stuttering* (e.g., Travis, 1927; Hill, 1944; Sheehan and Voas, 1954; Hutchinson and Watkin, 1976; Conture *et al.*, 1977; Freeman and Ushijima, 1978; McClean *et al.*, 1984; Conture *et al.*, 1985) and with stutterers' *fluent* speech (e.g., Starkweather *et al.*, 1976; Reich *et al.*, 1981; Watson and Alfonso, 1982; Metz *et al.*, 1983; Healy and Gutkin, 1984; Pindzola, 1986). One major difficulty with these previous efforts has been the lack of a consensus as to what constitutes normal movement coordination as well as a parallel paucity of quantitative measures to evaluate the alleged aberrations thereof (*see* St Louis,

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1979, and Andrews *et al.*, 1983, for reviews of the speech coordination abilities of stutterers).

In the last decade, kinematic analyses of complex natural movements have yielded critical perspectives on coordination underlying a variety of human neuromotor behaviours including gait (Grillner, 1975; Winter, 1984; Patla and Calvert, 1985), reaching (Morasso, 1981; Jeannerod, 1981, 1984; Abend *et al.*, 1982; Lacquaniti and Soechting, 1982; Atkeson and Hollerbach, 1985), hand movements (Viviani and Terzuolo, 1980; Cole and Abbs, 1986), as well as speech (Hughes and Abbs, 1976; Parush *et al.*, 1983; Gracco and Abbs, 1986). These studies have provided several robust indices of normal coordination that are common both to speech and limb movements. For example, natural multiple joint actions yield resultant motor outputs (e.g., the hand path from shoulder, elbow, and wrist actions in a reaching task) that manifest smooth trajectories with single velocity peaks (Morasso, 1981; Abend *et al.*, 1982; Kaminski and Gentile, 1986; Cole and Abbs, 1986; Gracco and Abbs, 1986). This ubiquitous generation of smooth single actions from multiple independent constituent movements is argued to reflect neural mechanisms of coordination (Abend *et al.*, 1982; Morasso, 1981; Cole and Abbs, 1986; Gracco and Abbs, 1986). Similarly, in the natural coordination of multiple kinematic actions for achieving a given motor objective, the absolute contributions of the individual constituents are covariable across repetitions, reflecting intermovement motor equivalence (Hughes and Abbs, 1976; Lacquaniti and Soechting, 1982; Winter, 1984; Cole and Abbs, 1986; Gracco and Abbs, 1986). Based on such measures, it is compelling to examine the claim that stuttering is an impairment of speech movement coordination.

While kinematic measures have been used to evaluate speech movements in stutterers, analyses have often been confined to movements of one speech structure (e.g., the lip or the jaw; *see* Hutchinson and Watkin, 1976; McFarlane and Prins, 1978). In studies where multiple speech movements were studied in stutterers, the number of repetitions and/or number of subjects have been very limited, albeit for technical reasons (Zimmermann, 1980*a*,*b*; Zimmermann and Hanley, 1983). The quantitative indices of coordination reported in the recent kinematic studies cited above require relatively high temporal and spatial resolution of movement transduction and, in most cases, a large number of repetitions. The present study involved kinematic analyses of upper lip, lower lip, and jaw movements during adult stutterers' fluent speech, with a high resolution transduction system that permitted at least 70 repetitions of the speech motor task per subject. These data suggested that certain temporal relations among multiple movements for stutterers were unlike those for normal speakers; even the perceptually fluent speech of these individuals manifested aberrant neural control processes.

## MATERIALS AND METHODS

### *Subjects*

Subjects for the present study were 6 adult male stutterers (mean age = 33 yrs) and 6 normal male adults (mean age = 32 yrs). For this investigation, assessment of the stutterers' dysfluency during a conversational speech sample included two objective measures which are widely used in diagnosis of stuttering: mean stuttering frequency (MSF), and mean stuttering duration (MSD) (Riley, 1972; Adams, 1980; Van Riper, 1982; Hayhow, 1983; Conture and Caruso, 1987). For the purposes of this investigation, stuttering was defined as sound/syllable repetitions and sound prolongations. For the 6 adult stutterers, MSF was 22 stutterings per 100 words (range· 7–35 stutterings per 100 words) while MSD was 615 ms (range: 150–1500 ms). All the subjects included in this study had negative histories for neurological, hearing, and speech problems, apart from the stuttering

### *Speech motor task*

Subjects repeated the utterance 'sapapple' requiring upper lip, lower lip, and jaw movement coordination for a sequence of oral opening-closing movements Emphasis or 'stress' was on the first syllable. This utterance was chosen because of the large data base previously acquired on these movement patterns (*see* Abbs and Gracco, 1984; Gracco and Abbs, 1986) We also wished to focus on a relatively large number of repetitions of a single utterance rather than more restricted samples of multiple utterances. The mean number of repetitions/subject was 156 for the stutterers and 147 for the normals. Subjects started each trial at rest with lips lightly touching. There were no syllable rate or movement requirements imposed on the subjects; the only instructions were to speak at a moderate vocal intensity level that was understandable 10 to 15 feet away. In essence, the procedure allowed for 'as-natural-as-possible' speech movements given the constraints of both the technique and the setting. All stutterers produced only *fluent* speech utterances during this task.

### *Apparatus*

Inferior-superior movements of the upper lip (UL), lower lip (LL), and jaw (J) were transduced using ultralightweight cantilever beams instrumented with strain gauges attached to a lightweight head mount (Barlow *et al.*, 1983). Transducers were attached midsagittally at the vermillion border of the upper and lower lips using an adhesive that does not interfere with normal speech movements (Müller and Abbs, 1979); the jaw transducer was placed under the chin in a location that yielded negligible artefact from skin movement. Each of the movement signals was digitized at 500 samples/s (12-bit resolution) on a Digital Equipment Corporation (DEC) PDP-11/44 computer and subsequently transferred to a SUN computer network for processing. All movement signals were digitally low-pass filtered (zero phase lag) using a two-pole filter of Butterworth design with a cut-off of 20 Hz. Instantaneous velocities were obtained digitally using three-point numerical differentiation. Because the movement signal obtained from the LL transducer reflected the combined action of the LL and the J, the J signal was subtracted digitally from the LL signal yielding a reflecting LL movement independent of the J. Hereafter, all reference to the LL signal is to the latter derived LL signal. An additional derived signal was the instantaneous interlabial distance (hereafter, the combined signal C). This combined signal is comparable to the resultant hand path in a shoulder, elbow, and wrist reaching or pointing movement, inasmuch as it reflects the instantaneous algebraic sum of the upper lip, lower lip, and jaw actions.

The transduced and derived signals from all trials were viewed on a SUN graphics workstation and specific events were marked with a cursor for subsequent quantitative analyses. As illustrated in fig. 1, the following kinematic events associated with the first 'p' in 'sapapple' were 'indexed' for UL, LL, and J movements: (1) *movement onsets*: time at which the positive-going velocity for the first closing movements exceeded 10% of the peak velocity; (2) *movement peak velocities*: the maximum velocities in the movement gesture; (3) *movement peak displacements*: maximum vertical displacements for the first closing movement.

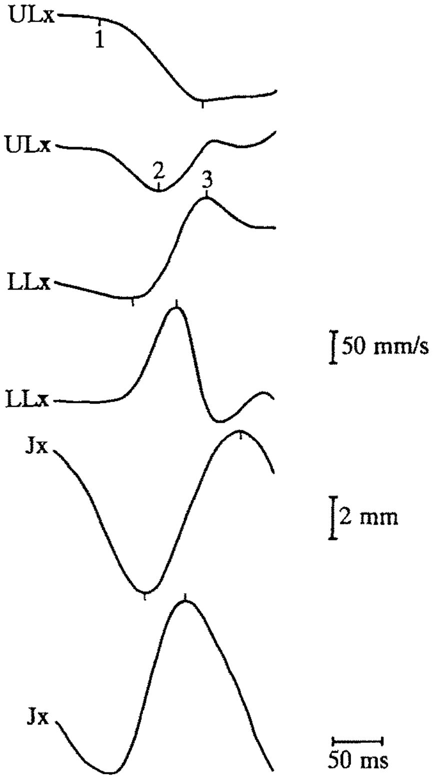

FIG 1 Upper lip (UL), lower lip (LL), and jaw (J) movement (x) and velocity (ẋ) traces for a single trial from one normal subject illustrating the following measures: (1) movement onset; (2) movement peak velocity; and (3) movement peak displacement. Similar measures were made for the combined (UL + LL + J) signal.

Whereas the speech acoustic signal was recorded on tape in parallel, acoustic analyses were not deemed justifiable because different patterns of speech movement can produce the same acoustic end product (Stevens and House, 1955; Hughes and Abbs, 1976; Atal *et al.*, 1978; Gracco and Abbs, 1986). As such, acoustic analyses were not considered to be ideal for studies of speech movement coordination.

## RESULTS

The kinematic analyses in this study were focused on objective indices previously reported to be aspects of normal coordination, including (1) combined movement smoothness (i.e., single-peaked velocity profiles), (2) motor equivalence covariability, and (3) timing and sequencing among the three constitutent movements. In addition, the present kinematic data also were analysed to address several earlier claims regarding general speech movement impairments in stutterers.

### *General kinematic characteristics*

Before presenting the specific results on measures of coordination in the fluent utterances of stutterers, it is useful to evaluate the overall characteristics of speech movements in this population. Previously it was reported that stutterers' speech

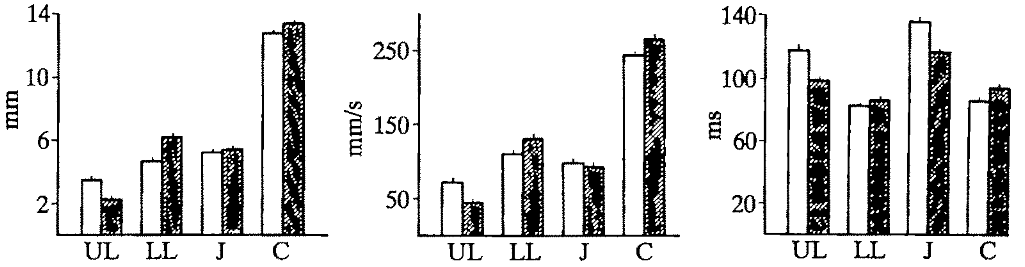

FIG 2. Bar diagrams of UL, LL, J, and C movement characteristics (displacement (*left*), peak velocity (*middle*) and duration (*right*) for the 6 stutterers and 6 normal subjects The vertical lines represent + 1 SEM. Normal subjects (open areas), stutterers (hatched areas).

movements during fluent productions of /p/ were reduced in velocity and amplitude from those of normal subjects (Zimmermann, 1980*a*). Fig. 2 summarizes the UL, LL, J, and C movement characteristics, including peak amplitudes, peak velocities, and movement durations. As is apparent, there are only small average differences between the two groups for movements of individual structures. For example, stutterers' UL displacements are slightly smaller than those of the normals, while their LL and J displacements are slightly larger or equivalent to those of normal. Similarly, stutterers exhibit lower peak velocities for the UL than those of the normals, yet peak velocities for LL and J are somewhat greater or equivalent to normal. Stutterers' movement durations are shorter for the UL and longer for the LL, and shorter than normal for the J. As shown, several of these movement characteristics are statistically different between the two groups of subjects. However, these individual UL, LL, and J movement differences would appear to be inconsequential given that comparable results were not seen in the net combined movement C (UL + LL + J, the total interlabial distance). It is apparent that C displacement, velocity, and duration for the stutterers are equivalent or slightly greater than for the normal subjects. While C displacement and velocity differences reached statistical significance due to the large number of degrees of freedom, the actual differences were small. Specifically, these differences were 1 mm for displacement (13 vs 12 mm, respectively) and 21 $\mathrm{mm \cdot s^{-1}}$ for peak velocity (264 vs 243 $\mathrm{mm \cdot s^{-1}}$, respectively). Overall, these data indicate that stutterers are not deficient in the range of their lip and jaw movements and jaw movements for speech, at least for this utterance, nor in the velocities of those movements.

### *Combined movement smoothness*

Based on previous observations of single-peaked velocity profiles as an index of multimovement coordination, UL, LL and J movements for oral closure were examined along with C, the resultant movement trajectory. Fig. 3 shows superimposed samples of UL, LL, J, and C velocity signals from 1 stutterer and 1 normal speaker; superimposed signals are shown for 4 repetitions of the speech motor task.

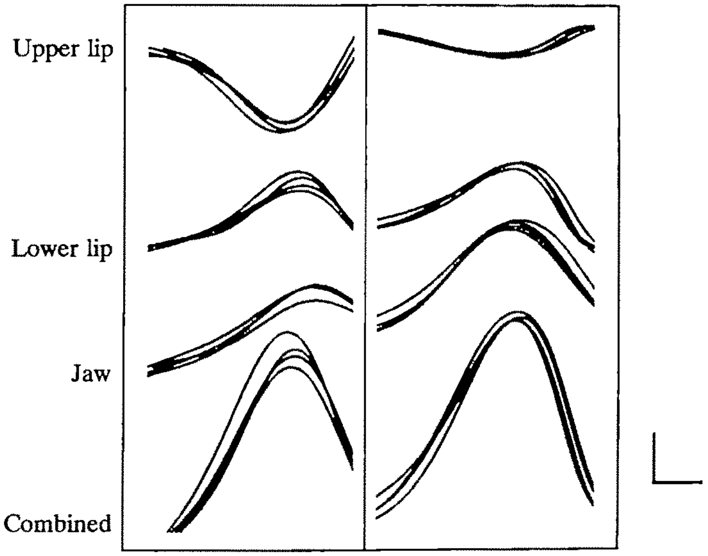

FIG. 3. Superimposed velocity profiles for upper lip, lower lip, jaw, and combined closing movements (4 trials) for the first 'p' in 'sapapple' for 1 normal speaker (*left*) and 1 stutterer (*right*). Individual movements and the combined signal for both the stutterer and the normal speaker manifested single-peaked velocity patterns. Horizontal and vertical calibrations represent 20 ms and 70 mm s$^{1}$, respectively

For every utterance produced by all 12 subjects (a total of 1815 fluent utterances), the velocity profiles were as shown in fig. 3; both the individual movements and the combined signal manifested single velocity peaks. Obviously this measure of coordination does not reflect inherent impairments in the speech movement coordination of stutterers, at least during fluent speech. Specifically, stutterers appear capable of organizing the individual spatial-temporal characteristics of UL, LL, and J movements in such a way as to yield a smooth resultant trajectory in the combined output.

### *Motor equivalence covariability*

Several different quantitative techniques have been used to evaluate the operation of motor equivalence covariability (*see* Hughes and Abbs, 1976; Gracco and Abbs, 1986). Fundamentally, it is necessary with these measures to determine whether the variability of the individual constituent movements is (1) independent, hence being additive in the combined action or, alternatively, (2) interdependent, yielding lower variability in the combined signal than that for the constituent actions. If the variability in the combined action is lower than in the constituent movements, this reflects the fact that the latter are coordinated or controlled interdependently; e.g., when the lower lip movement is disproportionately small, the jaw movement is disproportionately large, and conversely. Evaluation of motor equivalence coordination was focused on the variability in peak amplitude displacements associated with oral closure (measure 3; Methods). To compare variability of the individual UL, LL, and J movements in relation to the variability of the combined interlabial actions (C), normalized measures (coefficients of variation, CV) were used. With

CV measures (SD: mean), relative variability across movements could be evaluated despite differences in absolute displacements. The Table shows that the CV for the combined movement (C) was smaller than any of the individual movements for the 6 normal subjects, although in some cases these differences were small. For example, N3's CV for the C signal was slightly smaller than for the LL signal (0.113 and 0.116, respectively), and N5's CV for the C signal was slightly smaller than the UL signal (0.092 and 0.095, respectively). The Table also displays CV measures for each of the 6 stutterers. Similar to normals, the CV for the combined movement was smaller (S3, S4, and S6) or equivalent (S1 and S2) to the CV for individual movements. More specifically, S2's CV for the C signal equalled the CV for the LL and S1's CV for the C signal was equivalent to the LL (0.067 and 0.069, respectively). This equivalence would not appear to be indicative of an aberration in movement coordination, inasmuch as the variability in UL, LL, and J in these subjects clearly was not additive. For 1 stuttering subject (S5), the CV for the combined movement was slightly larger than that of the lower lip. It is obvious that, similar to the normals, the variance of the combined signal for any of the 6 stutterers did not increase proportionally with the larger magnitude of the interlabial distance, i.e., the variability of the UL, LL, and J were not additive in their contributions to interlabial distance variability. Apparently, this measure of multiple movement coordination, at least for the utterance under investigation, does not reveal consistent aberrations in stutterers.

TABLE COEFFICIENTS OF VARIATION OF THE PEAK CLOSING DISPLACEMENT FOR EACH SPEECH STRUCTURE AND THE COMBINED SIGNAL

*Controls*

| | *N1* *n* = *176* | *N2* *n* = *173* | *N3* *n* = *175* | *N4* *n* = *168* | *N5* *n* = *71* | *N6* *n* = *119* |
|---|---|---|---|---|---|---|
| UL | 0.204 | 0.303 | 0.149 | 0.125 | 0.095 | 0.251 |
| LL | 0.160 | 0.159 | 0.116 | 0.181 | 0.103 | 0.210 |
| J | 0.255 | 0.154 | 0.214 | 0.167 | 0.266 | 0.262 |
| C | 0.136 | 0.138 | 0.113 | 0.104 | 0.092 | 0.186 |

*Stutterers*

| | *S1* *n* = *153* | *S2* *n* = *172* | *S3* *n* = *175* | *S4* *n* = *124* | *S5* *n* = *137* | *S6* *n* = *172* |
|---|---|---|---|---|---|---|
| UL | 0.113 | 0.185 | 0.129 | 0.259 | 0.327 | 0.225 |
| LL | 0.067 | 0.123 | 0.149 | 0.132 | 0.078 | 0.124 |
| J | 0.197 | 0.172 | 0.114 | 0.206 | 0.139 | 0.138 |
| C | 0.069 | 0.123 | 0.090 | 0.105 | 0.083 | 0.086 |

n = number of movements, UL = upper lip movement, LL = lower lip movement, J = jaw movement; C = combined signal

### *UL, LL, and J movement sequencing*

It has been observed frequently that while magnitude characteristics of movement and muscle activity are variable across repetitions of a given motor act, temporal parameters are less subject to such influences (Winter, 1984; Grillner and Wallén, 1985). For example, it was shown recently that for oral closing ('p', 'm', or 'b'), UL, LL, and J movement onsets and velocity peaks were sequenced in that order, with less than 2% reversal across hundreds of repetitions (Gracco and Abbs, 1986). Additionally, the timing of these three movements was highly correlated (>0.95), even as durations of the overall oral closing gesture varied or with load perturbations of the lower lip (Abbs and Gracco, 1986). Likewise, for all 6 of the normal subjects in the present study, movement onsets were consistently sequenced UL-LL-J. As illustrated in fig. 4A for one of the normal subjects (N3), the velocity peaks of the UL, LL, and J also occurred in the same sequence as the movement onsets. However, by contrast, fig. 4B shows a different sequencing of UL, LL and J velocity peaks for one of the stutterers (S3). Indeed, the predominant pattern of sequences for movement onsets and peak velocities in 5 of the 6 stutterers was different from normal. Fig. 5 provides the UL, LL, and J sequencing data for all 12 subjects. As can be seen, only 1 of the 6 stutterers (S5) displayed the sequence of UL, LL, and J peak velocities that consistently characterized the normal speakers' movements. In addition to variations in UL, LL, and J sequencing, the stutterers also manifested considerable variability in their UL, LL, and J sequencing patterns, unlike the normal subjects. Specifically, as noted in fig. 5, variability in sequencing (percentage of sequencing reversals are shown in parentheses) ranged from 2.5% to 17.6% (mean = 10.5%) for the stutterers and 0–2.5% (mean = 1.2%) for the normal subjects. It is of note that although S5 exhibited normal UL, LL, and J sequencing, the frequency of sequencing reversals was double that of the most inconsistent normal subject. Interestingly, S5 was also the least dysfluent of the 6

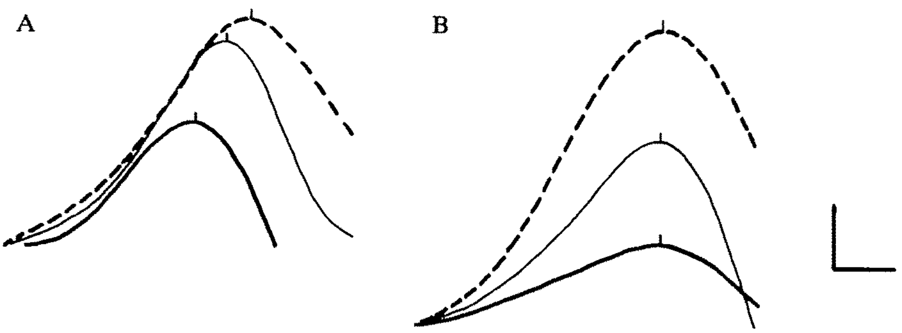

FIG. 4 First derivatives of upper lip (UL), lower lip (LL), and jaw (J), illustrating the temporal sequencing of peak velocities for the first closing movement during a single production of 'sapapple' by 1 normal speaker (A) and 1 stutterer (B) A tick mark has been drawn to indicate the time of UL, LL, and J peak velocities Horizontal and vertical calibrations represent 15 ms and 30 mm $s^{-1}$, respectively. UL $\dot{x}$ (thick line); LL $\dot{x}$ (thin line); J $\dot{x}$ (broken line).

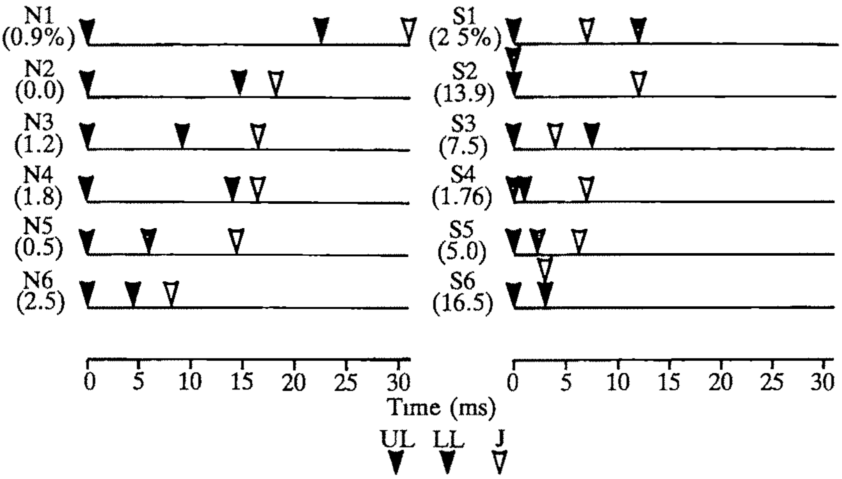

FIG 5 Schematic representation of the temporal ordering of UL, LL, and J peak velocities for each of 6 stutterers (S) and 6 normal (N) speakers Percentage of sequencing reversals are shown in parentheses for each subject.

stutterers during conversation. In addition to the sequencing differences, the intervals between UL, LL, and J movement onsets in the stutterers were remarkably shorter than 5 of the 6 normal subjects. The mean time between UL and LL peak velocities was 11 ms for the normals compared with 2 ms for the stutterers; the time between UL and J peak velocities was 7 ms for the normals versus 4 ms for the stutterers.

## DISCUSSION

Although it has been argued frequently that stutterers' abilities for speech movements are impaired on various temporal and spatial measures of coordination (Travis, 1927; St Louis, 1979; Zimmermann, 1980*a*, *b*, *c*; Andrews *et al.*, 1983), the fluent speech of these subjects appears to be similar to that of nonstutterers on two objective indices: (1) combined movement smoothness (in single-peaked velocity profiles) and (2) motor equivalence covariability. In other words, stutterers are capable of organizing the individual spatial-temporal characteristics of multiple speech movements to yield smooth resultant trajectories. Results of the present study do, however, indicate that the sequencing of constituent speech movements, a third index of multimovement coordination, is aberrant in individuals who stutter. Moreover, the stutterers manifested considerably more variability in their multimovement sequencing than normal. While only 6 stuttering subjects were investigated, the observation of aberrant and variable UL, LL, and J sequencing is particularly notable inasmuch as a consistent pattern was seen in normal subjects in this study and in more than 15 normal subjects examined previously (*see* Abbs and Gracco, 1986; Gracco, 1986; Gracco and Abbs, 1986). Another point that must be emphasized regarding these findings is that these aberrant sequencing patterns were observed in speech movements during *fluent* productions of a single-word utterance. One might hypothesize that the variable nature of this sequencing plus the shorter than normal intervals between the multiple movements reflect an inherently unstable situation, perhaps indicative of underlying neuromotor control problems in this population.

The aberrant sequencing in stutterers is interesting, particularly given that sequencing in normal subjects has been hypothesized to be controlled separately from movement amplitudes (Hughes and Abbs, 1976; Gracco and Abbs, 1986). Indeed, when unanticipated perturbations are introduced, these timing/sequencing patterns are not modified while adjustments in movement amplitudes and velocities are readily apparent (Abbs and Gracco, 1986). Such stereotyped sequencing of UL, LL, and J movements is similar to the timing stereotypy observed in motor actions such as chewing and locomotion (Lund and Olsson, 1983; Winter, 1984; Grillner and Wallén, 1985), commonly associated with subcortical centres. This timing/amplitude control distinction thus appears indicative of a functional separation within the speech motor control hierarchy for specification of movement and velocity amplitudes on the one hand and the specification of sequencing or timing on the other. The breakdown in sequencing in the speech movements of stutterers without parallel impairments in the covariable adjustments of movement amplitudes hence may reflect a neural impairment at a specific level of the speech motor hierarchy. More specifically, such a result may argue for a focal functional or perhaps neuroanatomical locus underlying the problem of stuttering for some stutterers.

As an additional indication of the selectivity of the sequencing differences in speech movements of stutterers, the results of the present study also indicate that stutterers generate UL, LL, and J movements with amplitudes, velocities and durations that are equivalent to or exceed those of normal speakers, at least for the utterance observed in the present study. Stutterers in the present study exhibited LL and J velocities that were somewhat greater than or equivalent to normal, UL velocities that were somewhat lower than normal, and C velocities that were similar to normals. Obviously, the speech movement control changes observed in subjects with known acquired brain damage such as speakers with Parkinson's disease (Hunker *et al.*, 1982), cerebellar problems (J. H. Abbs, S. M. Barlow and K. J. Cole, unpublished results) or spastic cerebral palsy (Kent and Netsell, 1975; Barlow and Abbs, 1984) (i.e., reductions in movement range, velocity, and increases in movement duration) are not manifest in the stuttering population. Normal ranges and velocities of stutterers' speech movements essentially enhance the finding of a very specific impairment in coordination/sequencing. That is, the observed aberrations in sequencing/timing are obviously not secondary to a general movement impairment. The observed normal movement amplitudes and velocities in stutterers are in agreement with recent speech acoustic signal measures (Pindzola, 1986; McMillan and Pindzola, 1986) indicating that stutterers' fluent articulatory dynamics are similar to or slightly exceed those of normals. It is of note, however, that present results do not support the data of Zimmermann (1980*a*) that stutterers' LL and J manifested speech movement velocities and displacements that were reduced compared with normal. Due to the constraints of cineradiography, the number of repetitions in Zimmermann's studies was very small and, as Zimmermann states, '... analysis of nine utterances from six stutterers ... must be limited' (p. 106). Additionally, it is not clear in Zimmermann's data whether the influence of the jaw was subtracted from that for the lower lip (*see* p. 98).

### *Earlier analysis of stuttering dyscoordination*

The selective aberration observed in the coordination of stutterers' speech movements may help to explain the relative failure in many previous studies to document consistently that stutterers manifest dyscoordination during fluent speech movements. However, previous investigations of stutterers' coordination abilities for nonstuttered speech movements have typically failed to exploit established procedures in motor control and neurophysiology. As a result, claims of impairments in coordination for speech in stutterers have been derived from (1) analyses confined to movements of only one speech structure (e.g., Hutchinson and Watkin, 1976; McFarlane and Prins, 1978) or (2) analyses of EMG activity without similarly complete kinematic analyses (e.g., McClean *et al.*, 1984). Unfortunately, the few investigations which have attempted to use quantitative indices of coordinated movement have been limited by technological constraints (Zimmermann, 1980*a*, *b*). In fact, most studies of coordination abilities for speech in stutterers have utilized indirect acoustic measures. For example, voice onset time (VOT) is one widely used measure in attempts to determine the timing/sequencing of stutterers' supraglottal and laryngeal movements. Results of VOT studies in stutterers have been equivocal (*see* Hillman and Gilbert, 1977; Metz *et al.*, 1979; Watson and Alfonso, 1982; Adams *et al.*, 1984; Healy and Gutkin, 1984), in part because the acoustic VOT measure often does not accurately and precisely reflect underlying speech movement events (*see* Caruso and Burton, 1987, for discussion of limitations of VOT as a measure of coordination).

While detailed analyses of coordination abilities for multiple movements in stutterers have been limited, there have been some previous descriptions of general coordination problems between major components (respiratory, laryngeal, and supralaryngeal) of speech production mechanisms in stutterers. For example, during instances of stuttering, aberrant sequencing of muscle activity and movement onsets (e.g., laryngeal muscle activity relative to chest wall movement) between different components of the speech production system has been observed during instances of adults' stuttering (Ford and Luper, 1975; Metz *et al.*, 1976; Yoshioka and Lofqvist, 1980; however, for stuttering in children, *see* Caruso *et al.*, 1988). Results of the present investigation thus augment these earlier studies; *even during nonstuttered speech, there appears to be little question that adult stutterers are impaired in their abilities to sequence the constituent motor actions for speech.* These select influences on sequencing may provide some additional insight into the neuromotor processes underlying speech movement coordination in stutterers.

### *Possible neural locus of timing-sequencing aberrations in stutterers*

The results of the present study appear to be generally consistent with the role of certain brain centres in motor sequencing and with suspected sites of neural aberrations in stutterers. Sequencing of movement has been hypothesized to be one function of the supplementary motor area (SMA) (Goldberg, 1985). A recent experiment on human subjects supports the involvement of the SMA in the timing/sequencing of limb movement. Roland *et al.* (1980) reported increases in regional cerebral blood flow (rCBF) in the SMA during a motor-sequence task involving the thumb and fingers, implicating the SMA in the sequencing of constituent movement in voluntary acts. It has been suggested specifically that the SMA plays a critical role in the complex timing inherent in speech acts. Investigations using EEG have demonstrated that activity over the SMA displays earliest onset (Deecke *et al.*, 1985) and maximum amplitude (Grözinger *et al.*, 1979) just before the initiation of speech. Although the EEG has limitations, it is argued to have greater temporal resolution than cerebral blood flow techniques (Wood, 1980; Moore, 1984). Other evidence that implicates the importance of the SMA in speech includes electrical stimulation of that area, which results in speech 'arrests' and 'hesitations' (Penfield and Roberts, 1959; Ojemann, 1983). Results of the above studies have been interpreted to suggest that '... the determination of the right moment to start and timing for *all* movements occurs in the SMA' (Deecke *et al.*, 1985, p. 152). Given the aberrant sequencing of movement onsets and peak velocities manifested by the stutterers in the present study—the only index of coordination which differed between the two groups—it might be speculated that the SMA may be involved in the disorder of stuttering. Present findings are interpreted to support the observations of Alexander *et al.* (1986) that an increasing corpus of data strongly suggests that the SMA plays an important role in the programming, initiation, and execution of movement. Interestingly, there is some limited evidence to suggest that as stutterers become more fluent, EEG (Boberg *et al.*, 1983) and rCBF (Wood *et al.*, 1980) activity increases in premotor cortical areas. Observations such as these, as well as hypotheses implicating anterior cortical involvement in stuttering (Yeudall, 1985) or impairments in stutterers' abilities for timing-/sequencing (Kent, 1983, 1984; MacKay and MacDonald, 1984) argue for additional consideration of the premotor cortical areas, particularly the SMA, as areas potentially involved in the disorder of stuttering.

Although instances of 'stuttering' have been associated with the lesions at various neuroanatomical locations (Jones, 1966; Canter, 1971; Rosenfield, 1972; Farmer, 1975; Quinn and Andrews, 1977; Helm *et al.*, 1978; Rosenbek *et al.*, 1978; Helm *et al.*, 1980; Mazzucchi *et al.*, 1981; Fleet and Heilman, 1985; Ludlow *et al.*, 1987), it is of special note that dysfluencies associated with lesions of the basal ganglia have been reported to be similar to developmental stuttering on various behavioural/clinical dimensions (Koller, 1983). The implication of the basal ganglia in the disorder of stuttering is consistent with recent data on the inputs to SMA. The SMA receives major connections from the basal ganglia, specifically from the globus pallidus and substantia nigra (Schell and Strick, 1984; Alexander *et al.*, 1986). Orofacial regions of the SMA, in turn, project to the primary motor cortex (area 4). Hence, while the basal ganglia per se are not thought to be associated with movement initiation (DeLong, 1971; Georgopoulos *et al.*, 1983) or 'sequential organization of programmed motor output' (Anderson and Horak, 1985), perhaps the increase in dysfluency for Koller's patients may relate to the powerful connections from the basal ganglia to the SMA. In a more recent investigation of brain lesions causing acquired stuttering (Ludlow *et al.*, 1987), the basal ganglia have been found to be affected more often in acquired stuttering than in other head injuries that did not result in speech dysfluencies. While it is important to emphasize that direct links between specific brain centres and stuttering cannot be drawn from the present study or the available literature, the aberrant sequencing of UL-LL-J peak velocities found in the present study apparently implicates suprabulbar rather than brainstem mechanisms in the disorder of stuttering. In fact, to our knowledge, no published evidence exists to support the hypothesized association between hyperactive brainstem reflexes and stuttering (Zimmermann, 1980*c*) during stutterers' naturally fluent (Caruso *et al.*, 1987) or adapted speech movements (Zimmermann and Hanley, 1983) nor during nonspeech tasks (Neilson *et al.*, 1979; Smith and Luschei, 1983).

Detailed instrumentation analyses of speech movement impairments generally have been restricted in the numbers of subjects. The present study is no exception. However, while results from such studies must be treated carefully, it is apparent that the more commonly used qualitative descriptions of motor impairments ascribed to given brain dysfunctions are not sufficient to permit meaningful interpretation. For example, while stuttering subjects manifest a certain form of speech movement dyscoordination, it is unlikely that this is the same aberration that might be found in patients with cerebellar disease (Kent and Netsell, 1975; J. H. Abbs, S. M. Barlow and K. J. Cole, unpublished observations). The above analyses thus indicate that there are several different levels and degrees of such impairments and simply to note that a given brain impairment yields dyscoordination or to provide some comparable qualitative description is not very useful. Such descriptions need to be extended with uncontaminated physical and biological measures. Otherwise, the terms used, as in the case of stuttering descriptions, yield few insights regarding underlying brain mechanisms.

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# PURE WORD DEAFNESS (ACQUIRED VERBAL AUDITORY AGNOSIA) IN AN ARABIC SPEAKING PATIENT

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## SUMMARY

A 38-year-old, right-handed Arabic-speaking male developed pure word deafness three days after myocardial infarction. He could recognize Arabic music and instruments but not words of songs; a radio broadcast from the Koran, but not the individual words; a male as opposed to female voice; Arabic and non-Arabic languages; and whether sentences were questions, exclamations, or imperatives. He discerned whether the speaker was emotionally neutral, happy, angry or sad. Contextual cues and reducing the rate of speaking aided verbal comprehension. Pure tone threshhold audiometry revealed mild bilateral sensorineural loss up to 2000 Hz and a moderate high frequency loss. Brainstem auditory evoked potentials were normal, cortical auditory evoked potentials abnormal. CT scan revealed bilateral infarcts subcortically just posterior to the left superior temporal gyrus and the right posterior superior and midtemporal regions. Neurolinguistic tests indicated that the deficit is prephonemic and not due to impairment of linguistic discrimination

## INTRODUCTION

Pure word deafness or acquired verbal auditory agnosia is characterized by an inability to comprehend and repeat speech, with preserved ability to identify nonverbal sounds. Reading, writing and speaking ability is also preserved. It was first described by Kussmaul (1877) and later by Lichtheim (1885). In its pure form, it is very rare. It usually evolves from or towards Wernicke's aphasia (Barrett, 1910; Ziegler, 1952; Klein and Harper, 1956; Gazzaniga *et al.*, 1973; Albert and Bear, 1974). It is described in patients with lesions deep in the left temporal lobe (Klein and Harper, 1956; Gazzaniga *et al.*, 1973; Albert and Bear, 1974; Denes and Semenza, 1975). However, most recent case reports, especially those with CT scan (Auerbach *et al.*, 1982; Coslett *et al.*, 1984) or pathological findings (Brick *et al.*, 1985) show bilateral temporal lesions occurring independently in time. In this

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case study of pure word deafness in an Arabic-speaking patient we analyse the neurophysiological, neurolinguistic and neuroanatomical findings.

## CASE REPORT

A 38-year-old Syrian male was admitted to the Coronary Care Unit with acute myocardial infarction confirmed by serial enzyme estimations and electrocardiography. On the second day of admission he developed multifocal premature ventricular beats treated successfully by lignocaine. After 24 h he had no arrhythmia and was haemodynamically stable; lignocaine was stopped. On the third day it was noticed that he was unable to respond appropriately to verbal commands, although he seemed to be behaving normally, speaking fluently and sensibly. He explained that he had a bad cold obstructing his hearing as the reason for not being able to understand the speech of others. With self-generated speech he seemed to make sense, but answers to questions were irrelevant, though fluent, grammatical and of appropriate vocal volume.

Examination revealed no neck bruits. All cranial nerves were intact, including normal optic fundi. No abnormality was detected in the motor system. All modalities of sensation were preserved, including cortical sensation. The tendon reflexes were symmetric and the plantar responses were flexor. His gait was normal.

Mental state and speech assessment was undertaken in Arabic, the only language the patient spoke. When he could not understand a question, it was written legibly in Arabic. He was right-handed, alert and orientated for time, place and person. Spoken speech was fluent, grammatically correct, with normal phrase length and no paraphasic errors. He listened to a tape with Arabic songs. He could recognize and appreciate music and musical instruments, but not the words of the song, although he guessed correctly that they were in the Arabic language. When he listened to a radio broadcasting a chapter from the Holy Koran, he recognized that it was from the Koran, but did not know the chapter, and could not understand the words. He was blindfolded and a series of oral tests showed the following correct scores: 4/10 for 'yes'-'no' questions; 4/10 for oral commands; 4/10 for repetition of single words, 2/10 for sentences, 6/10 for verbs, 0/10 for prepositions and 7/10 for the comprehension of proverbs. He was able to recognize all nonverbal sounds such as key jingling, telephone ringing, rustling paper, knocking on the table, hand clapping and animal sounds.

When he did not understand a specific verbal stimulus he could not tell whether it was a real word or a nonsense syllable complex. He was able to discriminate between a male and female voice and between Arabic and non-Arabic languages. He was able to tell when the same sentence was delivered as a question, imperative, or exclamation. He could also recognize when the speaker's voice was emotionally neutral, happy or angry. He could discriminate between laughter and crying.

In writing to dictation he scored 4/10 for numbers, 5/10 for single words and 0/10 for sentences; he made no mistakes in writing spontaneously, copying and answering written questions. Reading aloud and reading for comprehension were intact.

Praxis, right-left discrimination and finger identification were unimpaired. He made no mistakes in naming objects (tie, coat, shirt, glasses, newspaper), parts of the body (nose, eye, hair, finger) and geometrical shapes (triangle, rectangle, circle and diamond). He named colours correctly (red, green, gold, silver, yellow and blue). Simple addition was intact. He was able to draw a face and a house spontaneously, and he copied a three-sided cube correctly. He could draw a clock with the correct time Immediate and remote memory was normal. He was able to remember 3 numbers and the names of 3 cities, 3 min after presentation to him on a card. He also could perform a three-part command. He could remember the names of his children, his home and work telephone numbers and the town in which he was born.

## RESULTS

### *Neurophysiological findings*

#### *Pure tone threshold audiometry*

This revealed a mild, bilateral sensorineural hearing loss at frequencies up to 2000 Hz and a moderate high frequency loss (*see* Table).

TABLE PURE TONE AUDIOMETRY

| | *Threshhold (dB)* | |
|---|---|---|
| *Frequency (Hz)* | *R* | *L* |
| 250 | 35 | 35 |
| 500 | 30 | 35 |
| 1000 | 25 | 30 |
| 2000 | 10 | 15 |
| 4000 | 40 | 35 |
| 8000 | 50 | 70 |

#### *Brainstem auditory evoked potentials*

Waves I to V were of normal latency and amplitude bilaterally indicating intact brainstem auditory pathway function.

#### *Cortical auditory evoked potentials*

These were used to assess acoustic processing above the brainstem, using a Nicolet CA 1000 with a click stimulus of 2 Hz, 60 dB above hearing threshold with contralateral masking. Filters were set at 2–100 Hz with a sweep time of 200 ms; 256 responses were averaged on each run. The potentials were recorded from monopolar montages corresponding to T3–A1, C3–A1, C4–A2 and T4–A2 of the international 10–20 system. The same procedure was repeated twice on two separate days over a weekly interval. The potentials were compared with those from two healthy controls. A cortical potential response at 20 ms was obtained from the left temporal region (T3–A1) but not from the right (T4–A2) on stimulating either ear. The potentials in the left temporal region (T3–A1) and left central region (C3–A1) were higher in amplitude when the right ear was stimulated. These findings suggest the destruction of the right primary auditory cortex and probably right ear dominance.

#### *Electroencephalography*

The EEG showed long runs of moderate amplitude of theta-delta activity in the right temporal region suggesting a structural lesion.

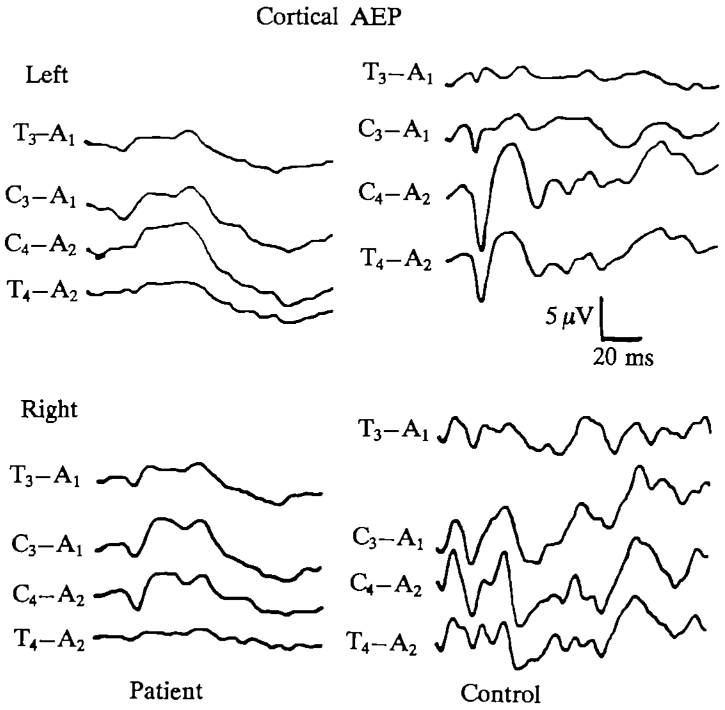

FIG. 1. Cortical auditory evoked potentials.

### *Click fusion and click counting*

These were used to assess the ability to discriminate short duration stimuli.

*Click fusion.* A Medelec M592a stimulator was used to drive an earphone. The double stimuli mode was used to give an accurate delay between two equal clicks applied binaurally. A click fusion time was established by the method of ascending and descending limits. He fused clicks at intervals of 16 ms; below this he could not detect distinct clicks. This was repeated 5 times and he was consistent at this range. Five normal controls fused clicks at 2 to 3 ms.

*Click counting.* This was performed on Nicolet CA 1000 evoked potential apparatus. A varying number of clicks over a period of 1 s were delivered binaurally and the patient was asked to count the clicks. He was inaccurate for rates greater than 2 Hz, in the 5 times the procedure was repeated. Five normal controls were able to count accurately at 8 to 10 clicks/s.

### *Comment*

These neurophysiological studies showed little evidence of peripheral hearing loss but an intact auditory pathway to the upper brainstem. Cortical auditory evoked potentials indicated destruction of right primary auditory cortex, but the severe deficit in temporal auditory acuity suggests that there should be another lesion on the left.

Other physiological studies showed changes in an ECG series consistent with acute anterior myocardial infarction. Echocardiography, performed twice, immediately after onset of comprehension difficulty and one week later, did not reveal left ventricular thrombus. There was mild hypokinesis of the left lateral wall of the left ventricle with good left ventricular function.

### *Neurolinguistic findings*

A number of linguistic tests in Arabic were directed towards a possible disorder in the discrimination of phonemes; all tests were performed with a native Arabic voice recorded on tape. Letters were shown on cards and he was asked to construct the heard syllables.

Vowel identification

| | | |
|---|---|---|
| ي | و | أ |
| ″Aa | Oo | Ee″ |

Score=97%

Fig 2 Three Arabic vowels used and the way they are pronounced

### *Vowel identification*

Arabic vowels were used; the way they are pronounced is shown in fig. 2. A total of 100 vowel stimuli were presented. The patient's score was 97%.

### *Phonemic discrimination/identification*

All items were in a consonant vowel combination. In this case the vowel was (AA). The initial stop consonant differed according to place of articulation (labial, alveolar and velar) or voicing (voiced/voiceless).

*Binary decision with a single distinctive feature.* This assessed voicing or place of articulation; the nasal component was not checked. Nine tests of 100 items each were administered. The items used and the appropriate way they are pronounced in English, with the score, are shown in fig. 3. The average score was 80%.

*Binary decision with two distinctive features.* The phonemes differed by two features instead of one. Three tests of 100 items each were given in the same way as above (fig. 4). The average score was 92%.

*Three-way decision for place of articulation.* In this test a triad of stimuli was chosen which shared similar voicing but differed by place of articulation. Two tests of 100 items each are shown in fig. 5. The average score was 61%.

*Ten-way decision.* The patient was given a choice of 10 consonants and asked to identify each of 100 items, with equal numbers of voicing and place of articulation as one of them. They were used in consonant-vowel or vowel-consonant combinations. The vowel was (AA). There were 10 errors in voicing and 40 errors in place of articulation. (fig. 6).

Binary decision
Single distinction

(A) Voice/voiceless

| | | |
|---|---|---|
| ما با | دا تا | غا خا |
| MA, $P_{PA}$ | DA/$T_{TA}$ | GA/$KH_{KHA}$ |
| 82% | 84% | 88% |

(B) Place or articulation
voiced stops

| | | |
|---|---|---|
| دا غا | دا ما | ما غا |
| DA, GA | DA, MA | MA GA |
| 78% | 78% | 74% |

(C) Place of articulation
voiceless stops

| | | |
|---|---|---|
| حا تا | با تا | خا با |
| $KH_{KHA}$/$T_{TA}$ | $P_{PA}$/$T_{TA}$ | $KH_{KHA}$ $P_{PA}$ |
| 82% | 76% | 80% |

FIG. 3 Phonemic discrimination. Arabic consonant-vowel combination' Binary decision—single distinction.

Binary decision
Two distinctive features

| | | |
|---|---|---|
| دا خا | غا با | ما تا |
| DA/$KH_{KHA}$ | GA/$P_{PA}$ | MA/$T_{TA}$ |
| 95% | 88% | 93% |

Av=92%

FIG 4 Binary decision with two distinctive features.

Three-way decision
Place of articulation

| | |
|---|---|
| ما دا غا | با تا خا |
| MA, DA GA | $P_{PA}$ $T_{TA}$ $KH_{KHA}$ |
| 56% | 66% |

$A_V$=61%

FIG. 5 Three-way decision for place of articulation

Ten-way decision

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ز | س | ن | ك | خ | غ | ت | د | م | ب |
| Pp/ | M/ | D/ | Tt/ | G/ | KH$_{KH}$/ | K/ | N/ | S/ | Z/ |

Score=10 errors voicing
Score=40 errors place or articulation

FIG. 6. Ten-way decision used in consonant-vowel or vowel-consonant combination.

The same neurolinguistic test was administered to 3 Arabic-speaking controls; they made no mistakes (100%).

*Comment*

Our patient clearly showed the following. (1) No difficulty in vowel discrimination. (2) Discrimination is best when there is both a voicing contrast and a place of articulation contrast, as in the data in fig. 4. (3) Discrimination suffers most when voicing is held constant and place of articulation varies, as in the data in fig. 5. (4) It does appear that place of articulation is more important than voice although some other features such as nasality were not checked.

*Neuroradiological studies*

CT brain scans were performed twice, the first at 2 days and the second at 5 days after he developed pure word deafness. They showed bilateral low attentuation areas in both temporal regions, compatible with recent cerebral infarcts. The lesion on the left in the posterior superior temporal gyrus evolved over 3 days to a smaller lesion in the subcortical area just posterior to the primary auditory area. The

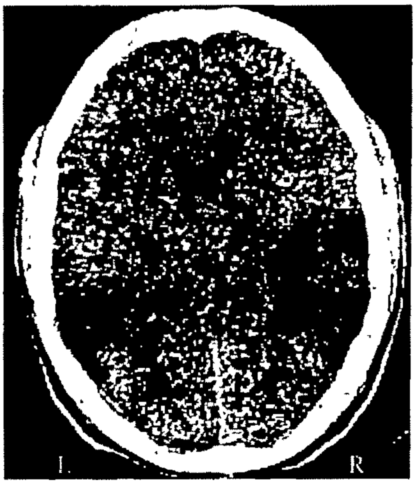

FIG. 7 CT brain scan showing bilateral temporal infarcts

lesion on the right was more extensive and involved the posterior superior and midtemporal gyrus, in addition to the posterior parietal region. This evolved after three days to a smaller lesion involving only the cortex of posterior superior and midtemporal regions (fig. 7). The bilateral lesions were in the border zones between middle and posterior cerebral artery territories supplied by the corresponding posterior temporal artery (Damasio, 1983).

## DISCUSSION

Our patient is unusual for three reasons. His inability to comprehend spoken speech was his only neurological abnormality; he exhibited 'pure' word deafness from the outset with no evolution from Wernicke's aphasia; and the pure word deafness was acquired because of bilateral, simultaneous and recent cerebral infarcts in the temporal lobes.

There was no evidence of generalized auditory agnosia, since he was able to recognize environmental (nonverbal) sounds. Our study does not support the contention in a recent review that auditory agnosia is found in all cases of pure word deafness (Buchman *et al.*, 1986). There was no evidence of cortical deafness because he was able to recognize sounds easily, and the pure tone audiogram showed only mild sensorineural hearing loss. This finding is described in pure word deafness (Lhermitte *et al.*, 1971). This syndrome was first ascribed to peripheral hearing loss by Freud (1891), but subsequent well-documented cases with autopsies showed a central origin (Goldstein, 1974). Our case was caused by bilateral lesions: cortical infarction destroying the right primary auditory area and geniculocortical fibres and a left subcortical white matter lesion of the posterior temporal lobe disconnecting Wernicke's area from the left primary auditory cortex, which was spared. These would support the disconnection hypotheses of Geschwind (1965) and Ulrich (1978). However, there are documented cases of pure word deafness associated with a single left temporal lobe lesion, presumably disconnecting Wernicke's area from the ipsilateral primary auditory cortex and interrupting transcallosal fibres from the contralateral auditory cortex (Gazzaniga *et al.*, 1973; Schuster and Taterka, 1926).

To our knowledge this is the first Arabic-speaking person described with this syndrome. A modified neurolinguistic test in the Arabic language was applied, taking into consideration some differences between Arabic and English phonemes. Few previous studies (Chocholle *et al.*, 1975; Semenza, 1975; Saffran *et al.*, 1976; Blumstein *et al.*, 1977; Auerbach *et al.*, 1982) examined the role of phonemic discrimination of natural speech stimuli in pure word deafness and other types of aphasia. Auerbach *et al.* (1982) proposed that a subclassification of pure word deafness can be made: Type 1 (prephonemic) is characterized by (1) a disorder in temporal auditory acuity causing particular difficulty with rapid formant transitions leaving vowel discrimination relatively preserved; (2) increasing the number of target distinctions would improve performance; (3) place of articulation would be the most vulnerable feature. Type 2, which is independent of temporal auditory acuity disorder, has a deficit in linguistic discrimination and is not prephonemic. The former is associated with bilateral temporal lobe lesions (M. Naeser, unpublished observations; Chocolle *et al.*, 1975), the latter with a left unilateral lesion (Chocolle *et al.*, 1975; Denes and Semenza, 1975). Our patient's neurolinguistic findings place him in type 1 and he had bilateral lesions.

Although pure word deafness has been attributed to tumour (Goldstein, 1948), infection (Goldstein *et al.*, 1975) and drugs (Donaldson *et al.*, 1981), most cases are due to stroke. In our patient the recent simultaneous infarction in both temporal regions could have been secondary to cardiogenic emboli to both posterior temporal arteries after myocardial infarction, although this seems unlikely. Therefore, because the simultaneous onset and the nearly homologous distribution would be unusual for embolism, and there were no arrhythmias on ECG monitoring and two normal echocardiograms, we believe that the most likely explanation for the bilateral simultaneous infarcts is hypotension during the myocardial infarction and subsequent hypoperfusion of these borderzone areas between the middle and posterior cerebral arteries.

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# BOOK REVIEWS

**1987 Year Book of Neurology and Neurosurgery.** Edited by Russell N. DeJong, Robert Currier and Robert M. Crowell. 1987. Pp. 486. London and Chicago. Year Book Publishers Price £38 50

In considering a review of the Year Book, which has been published since 1902, there are I feel only two things the reviewer requires to consider. First, does the continuing production of a *Year Book in Neurology and Neurosurgery* justify the hard work and expense involved and secondly, does this particular annual bear comparison with its predecessors? There are those of us who enjoy having the Year Book on our shelves and find it useful and helpful in seeking out key references for subjects of our own special interest and also, from time to time, browsing over the whole range of our specialty, reading every now and again in detail the critical reviews of the various papers reviewed by the editors. With the continuing expansion in publication of papers on the nervous system and its diseases, it is inevitable that even a Year Book must be highly selective in its material. I feel that the American Year Book adequately covers the subject and fully justifies continuing its existence. One of the major controversies of recent years has been the surgery of vascular disease of the brain and Dr DeJong, as editor, reviews the EC/IC bypass study and indicates where the key references are to be found.

As in previous years, the papers reviewed are divided into categories, some thirty in all, on a topographical, pathological and clinical basis. A section is devoted to recent publications on the acquired immune deficiency syndrome and no doubt, in subsequent years, this section will be considerably expanded.

I feel the Year Book has justified its publication over many years and the 1987 volume is well up to the standard of its predecessors. It is useful, comprehensive and stimulating and should certainly be on every departmental shelf and be available in every medical library. There will be many practising clinicians who also have benefited over the years from an annual subscription.

J. B. Foster

**More Dilemmas in the Management of the Neurological Patient.** Edited by Charles Warlow and John Garfield. 1987. Pp. 212. Edinburgh. Churchill Livingstone. Price £22.50.

Most of the articles in this book address aspects of neurological practice about which there is dispute as to the appropriate course of action. The editors have selected their subjects and authors well. Both neurology and neurosurgery are covered. The surgical topics should prove particularly interesting to medical neurologists. Neurologists do need to be clear about what their surgical colleagues feel they can offer to the treatment of gliomas, meningiomas and spinal epidural metastases. The authors generally show an admirable combination of lucidity and brevity. As a result you can comfortably read this book in the evening as a digestif. Despite its disparate subject matter, it avoids becoming yet another of those erratic and extortionate multiple author volumes which so frequently overburden our shelves, minds and library budgets.

Some of the articles are gems. McDonald reviews the flimsy evidence favouring steroid treatment for optic neuritis. He, with his own wide experience, only routinely recommends steroids for those who were already blind in one eye or when the optic neuritis is bilateral. Marsden debates the relative merits of L-DOPA and bromocriptine treatment for Parkinson's disease and casts doubt on the contemporary role of anticholinergic drugs. We hear that if he developed Parkinson's disease he would take prophylactic deprenyl 'with my tongue in my cheek'. No doubt his metaphor is tacit acceptance of the dyskinetic side effects that this might entail. The most useful article for me was by Lambert on choosing antibiotics to treat bacterial meningitis. As one of the noncognoscenti, I am usually overwhelmed by treatises on this subject written by microbiologists who, unlike Professor Lambert, prefer petri dishes to patients. Lambert brings crisp logic to bear on such issues as antibiotic choice when the organism is unknown, the duration of treatment, the role of repeated lumbar punctures, and the limitations of the newer cephalosporins.

I strongly recommend many of the other articles; for instance, Harrison on the pathophysiology of migraine, Jackson on the place of spinal surgery in treating traumatic paraplegia, Ross Russell on optic nerve gliomas, Compston on our (in)ability to predict the course of multiple sclerosis and Shorvon's discussion of whether anticonvulsant treatment might influence the natural history of a tendency to epilepsy. Shaw's calculations suggest that few motor vehicle accidents will be caused by drivers who have seizures following their craniotomies. His well-argued article, although long, usefully covers broader aspects of the relationship between epilepsy and fitness to drive. And it does so without a trace of the 'civil-service-speak' which so often flavours this subject.

This is an attractive paperback which is not too expensive. I only encountered one typographical error (p. 138) and the radiographs are adequately reproduced. The length and prose style of two articles could have been helped by ruthless editing. Usually the authors argue their controversies from balanced standpoints. This balance loses its poise to accommodate traces of a personal crusade in three articles. To their credit, these authors argue their cases sufficiently enticingly to increase, rather than decrease, my sympathy for their standpoints. But how much of the book really deals with dilemmas? A dilemma is an argument that forces one to choose between two alternatives which are both equally unfavourable; an argumentum cornutum. If the editors insist that their book is about dilemmas in neurological practice, I am grateful to their authors for showing which horn was less likely to impale me.

MICHAEL DONAGHY

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**Stroke.** By Clark H. Millikan, Fletcher McDowell and J. Donald Easton 1987. Pp. 341. Philadelphia: Lee and Febiger. Price $49.50.

After a drought period when little was written about cerebrovascular disease, the flood. There have been a large number of monographs in recent years all trying to fill the role of a working textbook for cerebrovascular disease. Most have been clinically orientated but have attempted to give sufficient background about the physiology and pathophysiology to enable the reader to see the logic or lack of it behind modern management.

The present well-produced text from three distinguished North American 'strokers' is in the same mould. Its cover is sufficiently wide to include vasculitis and other rare causes of stroke, and to devote chapters to young adults and children. The authors have not been firm enough with their self editing, however, and several topics appear more than once with little cross-referencing. Thus venous strokes appear three times yet nowhere are the underlying causes adequately discussed The diagnosis of venous occlusion is frequently very difficult and it is often the background general medical condition that brings it to mind. Binswanger's disease is dealt with in two separate sections. It is stressed that it is 'extremely rare'. However, CT and MRI scans frequently show diffuse white matter changes in elderly patients, and the problem of whether this represents Binswanger's disease needs to be more fully discussed. Other topics that I could not find include the role of lupus anticoagulant and how best to treat stroke events associated with mitral valve prolapse. On the plus side rehabilitation has a fair hearing.

The management style is North American. Anticoagulants are recommended. Aspirin, despite the consistent findings of numerous studies, is considered still to be sub judice. Surgery is the only treatment mentioned for subdural haematoma despite the success of conservative therapy in some cases. Carotid endarterectomy is reasonably assessed and it is good to see a conservative approach being promulgated for the asymptomatic bruit, even when major cardiac surgery is being planned. The ECIC bypass gets hardly a mention, a pity as the excellent international multicentre trial has much to teach us about stroke, as well as about how to advance treatment in this field.

Despite these quibbles I wish the book well, though it now enters a competitive field. There are enough strokes to go round. Whether there are yet enough physicians interested enough to buy all the books on strokes I doubt.

M. J. G. HARRISON

**Epilepsy—Electroclinical Syndromes.** Edited by Hans Lüders and Ronald P. Lesser, 1987. Pp. 399. Berlin and London: Springer. Price £69.00.

This is an elegantly produced book in the series *Clinical Medicine and the Nervous System*, the series editors of which are John Conomy of the Cleveland Clinic, and Michael Swash of The London Hospital. Lüders and Lesser were, they disarmingly tell us in their preface, originally trained as 'pure' electroencephalographers, but eventually also became epileptologists. Over the last 15 to 20 years neurologists have gradually come to terms with the International Classification of Epileptic Seizures, but many remain uneasy about the International Classification of the Epilepsies, modified and remodified, and last presented at the International Congress at Hamburg in 1985. Whatever one feels about the clumsy label, such as 'localization-related epilepsies', it has to be acknowledged that there is a real need for identifying groups of patients who have common pathologies and common prognoses.

Few would quarrel with the selection of clear-cut epileptic syndromes analysed in this book. There are excellent chapters by Barbara Westmoreland and Manuel Gomez on infantile spasms, and Warren Blume on the Lennox-Gastaut syndrome, which analyse the comparatively stereotyped way in which an immature central nervous system can react to chronic diffuse insults of various aetiologies.

The risk of partial seizures increases cumulatively throughout life as the brain is subjected to a variety of local pathologies. It is not surprising, therefore, that many of the remaining chapters refer also to the generalized epileptic syndromes commonly seen in childhood. There are chapters on neonatal seizures, febrile seizures, absence seizures, juvenile myoclonic epilepsy, progressive myoclonic epilepsy, and benign rolandic epilepsy of childhood, as well as useful summarizing chapters on simple and complex partial seizures and status epilepticus.

It is a characteristic of this book that the electroencephalograms are virtually without exception beautifully produced. The international system of electrode placement is used throughout, but I for one, and I suspect many other clinicians, will regret the passing of those helpful rubber stamp outlines of the head, showing the derivations I suspect that one has to be a full-time clinical neurophysiologist to feel entirely at home with a series of traces labelled Fpl-Al, etc.

The authors of each chapter have been given a clearly defined topic, and so there is remarkably little repetition within the book. Each chapter is a circumscribed and competent review of the field. I was surprised that the phenomenon of photosensitive epilepsy was not treated in great depth. The chapter on status epilepticus does not mention the considerable help a clinician may have from the cerebral function monitor of Prior and Maynard. However, omissions and unsupported statements are few, and I warmly recommend the book to colleagues interested in epilepsy.

ANTHONY HOPKINS

**Surgical Treatment of the Epilepsies.** Edited by Jerome Engel Jr. 1987 Pp. 746. New York. Raven Press. Price $144 00.

This book presents material given at a meeting held in the Spring of 1986 at Palm Springs, California, to mark the centenary of Horsley's paper describing three intracranial operations for epilepsy. One hundred years later this topic is still controversial and for many practitioners in the relevant clinical disciplines, surrounded by mystery and prejudice. The participants at this meeting came from 53 centres throughout the world. They were deliberately chosen to include representatives of all the relevant clinical disciplines and the whole spectrum of surgical practice. Virtually all the participants were senior and internationally respected specialists in their field.

The book is divided into different sections dealing with historical aspects and the aims of surgery, evaluation of extracranial and intracranial methods of investigation, reviews of surgical treatment, and assessment of the results. Finally, there are three appendices which deal with presurgical technique, presurgical evaluation and a fascinating section dealing with the relevance of findings in experimental epilepsy to surgical treatment. These topics are all covered in depth with details of neurophysiological, neuropsychological and surgical technique. Newer methods of brain imaging are adequately discussed.

Each of the contributing centres was asked to provide details about the patients that they treated so that there are a number of valuable summary chapters based on these data. Also of value are commentary chapters which embody the discussions which took place at the meeting after the topic had been presented. Finally, each section is terminated by a chapter which attempts to answer the question posed by that section; for example the section on extradural evaluation finishes with a chapter entitled 'When are noninvasive tests enough?'.

The investigation of patients with chronic epilepsy for surgical treatment and the surgical techniques which can be employed to treat them is a complex issue which will never be an easy one to resolve. This book is the first since the previous Raven Press publication 12 years ago to give a concise and realistic account of this topic. It will be invaluable to all neurologists, neurophysiologists, neuropsychologists, neurosurgeons and neuropsychiatrists concerned with the evaluation and treatment of patients seeking a surgical solution to their epilepsy. Hopefully, it will not only be on their shelves but also in their hands.

C. E. POLKEY

**Northfield's Surgery of the Central Nervous System,** Second edition Edited by J. D. Miller. 1987. Pp. 893. Oxford: Blackwell. Price £120.00.

It is now 14 years since the late Mr Douglas Northfield published his *Surgery of the Central Nervous System*—the only general neurosurgical textbook to be written by a British neurosurgeon. This book was a monument to the lifetime experience of a single surgeon and a testimony to his energy and determination. Although it was clearly time for a complete revision of this remarkable work, such revision could now hardly be undertaken by one man. Accordingly the work has been carried through by a team of 7 neurosurgeons, 2 neurologists and a radiologist led by Professor J. D. Miller of Edinburgh. As the greater part of the work was undertaken by 7 specialists in Liverpool, this revision might be aptly re-termed 'The Liverpool Textbook of Neurosurgery'.

The structure of Northfield's original work has been retained, and preserved within this book are many of his original passages and some of his original illustrations. Nevertheless the present team have greatly expanded the original text and have brought it up to date in a manner which can scarcely be faulted. Every aspect of neurosurgical practice is covered and this volume will continue to serve as the standard guide to neurosurgery in this and many other countries. It is well bound, well illustrated and well laid out. The typeface is as clear as the text. Although at £120 it can hardly be described as cheap, it will be an essential purchase for every neurosurgeon trained in the British tradition and few, if any, of the purchasers will regret buying it. This reviewer can only make one criticism of this volume. It is that the single glaring fault of the original work has not been corrected, perhaps as a result of misplaced economy on the part of the publisher. The fault is this: the old fashioned system of references has been retained giving neither the titles of papers nor their full pagination. This means that one simply cannot tell whether a reference that one might be interested in is worth looking up. At first sight this may appear a trivial criticism but it is an important matter in a book which will become a standard source of reference. One can only hope that the publishers will correct this matter in the next edition—an edition which is certain to become necessary in the course of time. In all other respects Professor Miller may be justifiably proud of this work. As always, those chapters written by himself personally are a model of clarity and a delight to read.

R. S. MAURICE-WILLIAMS

**Concepts in Neurosurgery.** Volume 1. **Neurosurgical Critical Care.** Edited by Fremont P. Wirth and Robert A. Ratcheson. 1987. Pp. 253. London: Williams and Wilkins. Price £41.00

This is the first of a new series on 'Concepts in Neurosurgery' produced by the Congress of Neurological Surgeons. This volume on *Neurosurgical Critical Care* aims to provide basic scientific knowledge and theory and to relate this to 'practical neurosurgical concerns'. Of the 27 authors of the 11 chapters, 26 are from centres in the USA.

All systems are systematically and comprehensively covered. Although a large part of the book reads like a textbook of physiology, in each chapter the authors successfully link basic theory with clinical problems. Monitoring techniques repeatedly feature yet, surprisingly, clinical examination is completely omitted. The editors comment on this major deficit in the preface, but proffer no explanation—perhaps this topic will appear in a future volume. Tighter editorial control could have prevented the continual repetition of subjects. Acid-base balance, diabetes insipidus, inappropriate ADH secretion, corticosteroids in brain oedema and hyperventilation for raised ICP are examples of topics cropping up in at least two different chapters.

Inevitably questionable statements exist. In the chapter on 'Infection' the authors state that mortality rates from brain abscess still range from 20 to 40%, yet the paper they quote is based on a 15-year study published in 1981! Although Acyclovir is mentioned as the possible future drug choice for treatment of herpes encephalitis, the recommendation to use Vidarabine reflects the inevitable North American slant. Atrial natriuretic hormone has been recognized for 5 years yet is omitted in the chapter on 'Fluid and Electrolytes'.

These are small points. I am sure this book will appeal not only to those training in neurosurgery but to anyone connected with critical care.

K. W. LINDSAY

**Advances in Ophthalmic, Plastic and Reconstructive Surgery.** Volume 4, **Blepharospasm.** Edited by Stephen L. Bosniak and B. C. Smith. 1985. Pp. 429. New York: Pergamon Press. No price.

It is fitting that this multiauthor monograph on blepharospasm should begin with a reprint of John Warren Henderson's extensive review on essential blepharospasm first published in 1956. Up until that time only 35 cases had been reported and the prevailing view was that if the condition existed at all as a discrete entity then it was almost certainly psychogenically determined. However, within these early piecemeal descriptions one can find a clear account by Henri Meige in 1910 of 'spasme faciale bilateral et mediane' in which he describes the association of tonic involuntary eyelid closure with lower facial and jaw movements It is difficult to understand why this lucid account was not picked up in the neurological literature to a greater degree and why at the same time equally esoteric phenomenological rarities blossomed. Even Henderson's meticulous account of 135 cases seen at the Mayo Clinic between 1925 and 1954 failed to influence medical opinion greatly and most of my teachers were brought up on the view that isolated eyelid spasms were some sort of conversion neurosis. Therapeutic advances in Parkinson's disease and the possibility that neurochemical abnormalities without demonstrable histological lesions might underlie other movement disorders led to an intensive reexamination of many hitherto neglected disorders. As a result, personal series of more than 200 cases of essential blepharospasm are now by no means rare in movement disorder and ophthalmological circles and the Benign Essential Blepharospasm Foundation in the United States is flourishing as a support group and grant-giving body. The fact that publishers are prepared to risk a volume of more than 400 pages devoted to this condition reaffirms this view. It is also probably not a coincidence that its appearance coincides with the advent of the use of botulinus toxin A injections into the eye muscles as the first effective, relatively noninvasive therapy. The book begins with a number of sound but rather unstimulating reviews of blepharospasm through the eyes of neurologists and here—as in most of the book—there are perseverative duplications on almost every theme. The phenomenology is now well developed and abnormalities of the duration, amplitude and excitability cycle of recovery of the blink reflex have been reported. Little is known, however, about the genetics of the condition and even the site of the presumed neurochemical dysfunction in the brainstem is controversial. The relation of local ocular trauma to the pathogenesis of the condition is not discussed nor are the possible associations with myasthenia gravis and tics. Despite the length of the book there is no chapter on secondary causes of blepharospasm or tonic inhibition of levator palpabrae (apraxia of eyelid opening) or a detailed discussion of reflex blepharospasm. The natural history of the disorder is also badly covered, whereas five chapters are devoted to the generally disappointing drug treatment of the disorder. There is an interesting and thoughtful chapter on the use of electromyographic biofeedback which, despite generally disappointing results so far, is worthy of further exploration. There is a chapter on the use of hypnosis as treatment in which the patient is told that he will find it increasingly difficult to open his eyes during the induction period, a request which many patients would find only too easy to carry out! The paper on acupuncture recommends that the liver and gall bladder meridians be used and promising results are reported. There are three chapters on the psychological and psychiatric aspects of blepharospasm where it is suggested that patients have a rigid histrionic personality, that blepharospasm is a conversion disorder rather than an adult onset focal dystonia and that stressful life events are almost invariable triggers. The remainder of the book discusses the use of botulinus toxin and the various surgical approaches including percutaneous thermolytic fractional destruction of facial nerve branches, facial neurectomy and myectomy. As befits a book designed primarily for an ophthalmological audience considerable attention is given to the surgical details of all these procedures. The results, however, are not assessed critically and it would seem that in those patients who are disabled despite an adequate trial of botulinus toxin, myectomy stands a better chance of a good result than section of the nerve.

For a neurologist with a special interest in movement disorders, the most instructive parts of the book will be the detailed accounts of the surgical approaches to refractory blepharospasm, the risks and the results. Overall the subject is not sufficiently advanced to warrant a monograph and the available facts could easily be summarized in a single review article The other three volumes in this series deal with ptosis, the ageing face, and the lachrimal system. Perhaps in a hundred years' time these volumes will become collectors' items hailed as pioneer tomes in established specialities. In five years' time, however, I suspect that those copies not safely housed in the largest of medical libraries will be available at secondhand book sales at bargain prices.

A. J. LEES

**Neuroendocrinology.** Edited by S. L. Lightman and B. J. Everitt. 1986. Pp. 622. Oxford Blackwell. Price £60.00.

This is a multiauthor review of central and peripheral neuroendocrine processes. It provides a wide coverage of the basic neuroendocrine physiology, mostly directed at experiments involving rodents, although human and subhuman primate data are discussed where these are available. Unfortunately, there are only brief references to the alterations found in pathological conditions, and the neuroendocrine implications of disease states are dealt with much more briefly than the subprimate physiological topics Indeed, one problem of variable severity in different chapters is the occasional failure to differentiate between findings in different species and in particular to distinguish between the relevance to man of the mechanisms discussed and observed in rodents. Such important species differences are dealt with clearly in some chapters such as reproduction and prolactin, but poorly in a number of others. The chapters are conventionally arranged, and some deal generally with overviews of several systems such as the significance of opiates and endocrine rhythms, but others review special topics such as brain steroid receptors, somatostatin, thirst, hunger, circulation and salt and water excretion. The level of discussion in these overviews is well maintained; the most successful sections are those on reproduction, hunger, growth hormone, prolactin and thirst, but some other chapters contain important inaccuracies or deficiencies There appears to be a lack of a consistent policy with regard to references in the text. The authors seem not to be sure whether this book is meant to be didactic like a textbook, with only a few major review references, or a specific and detailed review of each topic with a fully referenced text, and as a consequence variable styles are seen.

The general impression remains that this book is largely successful and may be recommended as a good and interesting survey of neuroendocrine progress in this rapidly advancing field. It is more complete for animal than human physiology. The clinical implications and aberrations are not adequately covered, and the book will be of more interest to physiologists than to the clinician.

G. M BESSER

**What the Hands Reveal about the Brain**. By H. Poizner, E. S. Klima and U. Bellugi. 1987. Pp 236. London: MIT/Bradford Books. Price £22.50.

This marvellous book can be read at one sitting. It describes six neuropsychological cases of acquired brain damage. Three are left hemisphere damaged patients. Three are right hemisphere patients with damage of various cortical sites. Scans of all patients are included in the book. The left hemisphere patients show predictable patterns of language disorder, including dysfluent, uninflected speech with reasonable comprehension (agrammatism), phonemic processing disorders and fluent paragrammatism. The right hemisphere patients, too, show predictable disorders; visual object agnosia, apraxic disturbances and problems in spatial processing (including neglect). In each case, the presenting symptoms are precisely those we have been led to believe should occur given the site of damage. The cases are meticulously described, with full nontechnical descriptions of tests and behaviours and include much important detail showing how these people are affected in their everyday life. The copy editing is excellent (I could find only one real error; it concerns an implication that Broca's aphasia can implicate the parietal lobe) and the book is widely, clearly and necessarily illustrated.

What, you may ask, makes this such a special report? Only this· each of the cases is a born-deaf, native user of American sign language (ASL), raised and living with other native signers. These are unique cases which cast an extremely clear light on the relationship between brain structures and language. They convince me, as some studies of ASL have failed to do, that ASL is, indeed, a language, rather than a gestural system, and that in those for whom it is a native language it is localized and organized in precisely the same fashion as spoken language. This is not to deny the likeness of many of the lexical and referential structures in ASL to those we can use in nonverbal communication, but it is to deny that they are handled in a 'nonlinguistic' way by ASL speakers. (The citation in this book, of recent studies by Laura Pettito, is extremely apt in this regard.)

The pattern of breakdown of language, mapped by these cases, owes little to its auditory or even articulatory structure, nor (as some have claimed) to the fine temporal structuring that spoken language seems to demand. ASL is structured in space and time and does not use articulatory mechanism. What is important is that, like spoken language, it is hierarchically organized, with levels corresponding to syntactic, morphological, lexical, phonemic and phonetic. These can be as independently affected by cerebral insult as they can in hearing people.

So it is in these patients that we find some beautiful dissociations that allow us to come to conclusions that would have been unreachable otherwise. Thus a right hemisphere patient who is apraxic for making gestures (make the sign that indicates 'you must stop') can say 'stop' in ASL. In ASL the word 'stop' is not the same hand movement as the gesture the policeman makes to stop cars. And the complementary dissociation occurs in the left hemisphere patient with word-finding difficulties. Apraxia dissociates from aphasia even in individuals who use hand-signing as a native language. One of the right hemisphere patients shows pronounced left-sided neglect. But this patient's signing is excellent, though one handed (in ASL all signs are produced symmetrically, by both hands). The neglect patient, in describing a spatial layout, signs appropriately, but indicates the items he is describing in a 'neglected' fashion. That is, his description ignores items on the left of (imagined) space and he 'bunches up' his signs in the right of the 'field' of signed description.

One of the many marvels of this book is the elegant and efficient way in which the phonocentric reader is led into the world of the ASL speaker and the particular spatial and movement devices that are used to indicate different linguistic structures. Two aspects of this strike me as especially noteworthy. One is the detailed, thoughtful adaptation of the Boston Diagnostic battery for use with this tiny population (and elderly control subjects) Tests for sensitivity to phonological similarity (where one might have to pick the picture that rhymes with a given picture) are replaced by tasks where the same handshape component is present in the target as the probe picture. On this basis, in ASL, 'cow' and 'telephone' rhyme. Similarly great care is taken over semantic judgements. In ASL there can be sign similarities between cognate words—so that 'chair' and 'sit', for example, use similar handshape movements. But 'book' and 'read' do not, so the Boston item that asks 'what is a chair for?...' is replaced, for the ASL speaker, by 'what do you do with a book?'

The second real insight, for me, was the critical importance of an imaginary plane, about the size, shape and position of an aircraft passenger's food tray, in the enactment of ASL. This is necessary in the detailing of indexed relations, where pointing to different positions indicates who (or what) is being referred to. In ASL, this plane can be used to disambiguate sentences like 'he gave it to him' which in English tend to be clarified (if at all) by a head nod or by further elaboration. This plane can be used for the recall of listed items, too—it seems to be an essential device for maintaining order and is, if anything, more effective than our strictly spoken, serial, temporally organized system. I would love to know more about how, when and why it works. It is intriguing that it is in disturbances of the use of this system that the performance of these 6 patients suggests some rather ambiguous patterns of functional localization. The apparently 'agrammatic' patient, for example, though very impaired in the production of morphologically and syntactically complex utterances, was bad at *comprehending* morphologically complex items, but not at interpreting syntactic differences that used the (syntacticospatial) plane.

Now I feel like the person who has been to the play before and whose enthusiasm risks spoiling the pleasure of the audience by telling everyone what happens There are many many intriguing findings in this book and it is one of its many virtues that, in reporting work very much in progress, it encourages speculation and rethinking of basic issues in cognition and language at (literally) every turn

A word of warning. ASL is a local not a universal language. It is not used by British deaf people. On the whole, the teaching of the deaf in Britain has proceeded along oral lines, encouraging the use of lipreading with residual hearing Signing has not been encouraged. As a result, the status of native British sign language (BSL) is insecure and its use—even research into its structure and function—carries sociopolitical implications that are not present for (most) native ASL users. More important still, the two sign languages are not formally related, as are British-English and American-English. ASL probably derives from French sign language, BSL not. So this book cannot be used as a handbook for examining all deaf people with neurological damage. Instead, for the non-ASL speaking researcher, who is unlikely to encounter an ASL aphasic or agnosic, the book offers an object lesson in the careful analysis of a linguistic system—whatever its provenance and modality—and its equally careful examination in cases of neurological breakdown It is a model book with a modular message; modality doesn't define language. (And if you think you can't pun in ASL—read the book!)

RUTH CAMPBELL

**From Schema Theory to Language.** By M. A. Arbib, E. J. Conklin and J. Hill. 1987. Pp 253. Oxford University Press. Price £35.00.

There is probably an increasing number of brain scientists who feel that it is no longer admissible to shun Artificial Intelligence (AI) altogether. To the uninitiated, *From Schema Theory to Language* offers an excellent opportunity to learn what is going on in this field. The expert, on the other hand, may find in its pages incitement to conceptual clarification of several issues, as well as a technology apt to enhance empirical investigation of cognitive processes with special regard to the pathology of higher nervous functions such as visual perception and language.

In harmony with current AI trends, the authors criticize the principled ignorance of brain research which characterized earlier approaches in cognitive science. Their purpose is one of filling the gap between top-down (AI) and bottom-up (neuroscience) modelling of cognitive processes by resorting to a unit—*schema*—that might be reduced both to a section of a computer program and to the activity of a neural network close to Hebb's notion of cell assembly.

Although dispensing themselves from giving a historical account of the concept of schema as the basic unit of mental representation of the world, the authors clearly state and exemplify their own interpretation of the term in the first part of the book. Readers with a biological background will probably appreciate that, contrary to a deeply-rooted tradition in cognitive science, Arbib *et al.* explicitly assert that 'a schema is both a process and a representation' (p 7). Schemata, indeed, are seen 'as being as much procedural (program-like) as declarative (data-like)' (p. 17). In declaring their own commitment to a theory stressing the sensorimotor roots of language, the authors indicate in Jackson the forerunner of an approach that 'emphasizes the overlap of linguistic and nonlinguistic functions' (p. 32). As we shall see, mention of this sort of overlap is the first indication of an ambiguity that reappears on several occasions throughout the book. The remainder of Part I introduces and exemplifies concepts and models of parallel computation.

In Part II, 'process' models of linguistic functions, that is, models conforming to the functional analysis that characterized Luria's approach, are contraposed to 'connectionist' models of earlier neurolinguistics. The authors argue that only the former can deal properly with the complexity of language processes. Furthermore, 'process' models are maintained to befit AI simulation and to permit a better use of neurological data for the understanding of language in the normal brain, they are also sympathetic to the idea, advocated by Arbib *et al.*, of a sensorimotor nature of semantic representation. An AI model of language comprehension is next described The consequences of selective 'lesions' in the model are considered with reference to the symptomatology of Broca's aphasia.

In Part III, the authors reiterate their strong opposition to 'autonomous' theories of language processing and place Piaget against Chomsky They consider language as a 'communicative device' (p. 106). Given the import of this claim, and to avoid misunderstandings, the reader should have perhaps been told at this point what kind of evidence would support their position and what kind of model would correspond to it It is not completely clear whether the model of language acquisition described in this part of the book meets this requirement.

Part IV is devoted to language generation in scene description Since this is where the above mentioned ambiguity is easier to discern, this part is worth closer consideration.

Two phases of generation are envisaged. a deep phase, *selection* (what to say and what not to say), and a surface phase, *realization* (how to express what has been selected). Input to natural language generation is held to be a symbolic representation of the visual information in a picture (p 159)

Unfortunately, by making use of the puzzling term 'symbolic' the authors seem to lapse into the style of explanation of cognitive processes they had proposed to dispute.

In this model, selection for communication is made on the basis of salience. There are low-level factors of salience, such as size and centrality of an object, and high-level factors. The latter are subdivided in extrinsic (unusualness) and intrinsic. Intrinsic factors are said to be personal and professional association with the object, cultural association and, quite unexpectedly, movement. Objects are listed in a register in which they are ordered on the basis of their salience. Two classes of subregisters contain a list of properties and a list of relations of each object, respectively, both ordered according to salience. These items are used by the deep-generation system, called GENARO, whose job is one of providing the realization-specifications needed for the second phase of language generation, that is for the formation of a natural language utterance. This phase, which is held to be 'the part of the generative process that is truly language specific' (p. 171), is operated by a system called MUMBLE.

Realization-specifications are chunks containing four kinds of elements: objects, properties, relations and rhetoremes. The latter have a rhetorical function only; they represent the deep components corresponding, for example, to introductory segments such as 'This is a picture of' in the surface structure. The internal organization of such chunks, as well as their concatenation in the description of the scene, depends on the priorities set by salience ratings, on the relationships between a selected item and other objects in the scene and on a set of rhetorical rules relative to the introduction of the message, the condensation of several chunks into a single one and the formulation of concluding remarks.

MUMBLE consists of a pair of transducers. The first lexicalizes the elements of realization-specifications in the same order in which they are produced by GENARO; the second organizes the output text following the rules of a grammar.

The question here arises of what is cognitive in language generation and what is not. In some respects, the authors' decision seems to be straightforward. By applying the term 'transducer' to the component responsible for the execution of 'that part of the generation process that is *truly language specific*' (p. 171, italics added), they apparently deny cognitive status to language. All information needed for surface generation is already present in realization-specifications supplied by GENARO and blindly translated into an utterance by MUMBLE. The administration of rhetorical rules falls within GENARO's competence. Even details such as the choice between definite and indefinite articles are not autonomously computed by the language-specific component of the system but predetermined by GENARO (p. 173).

This approach is tantalizing vis à vis the more or less covert linguistic chauvinism that still characterizes much of cognitive science, but there are passages in the book that seem partially to disavow this radical choice. For example, although not without a shade of perplexity, the authors assign to the language-specific component the task of choosing among alternative syntactical forms which are not semantically equivalent (pp. 177–178). Further on, in admitting that there is a grey area in which it is difficult to distinguish whether a given fact is or is not linguistic (p. 181), they refer to rhetorical aspects that elsewhere they unhesitatingly attribute to the prelinguistic phase of language generation.

Now nobody would dispute the existence of grey areas between cognitive and noncognitive ascriptions and between linguistic and nonlinguistic processes. Such areas, however, are most prone to engender equivocation. Does reference to the 'overlap of linguistic and non-linguistic functions' (*see* above) mean that the deep phase of language generation is viewed by Arbib *et al.*, if not 'truly language specific' as the surface phase, still in some sense linguistic? This is not only a terminological issue. More to the point, MUMBLE is said to transduce from a 'symbolic representation' (a 'meaning') into an utterance (p. 173). This kind of representation seems to be identical with the realization-specification, that is said to contain 'all and *only* the information' needed for surface generation (p. 171, italics added). What kind of information is left out? What does the term 'symbolic representation' *exactly* mean? What would be the putative neural code for this type of representation?

The last question might appear otiose and, to some people, not to be asked. Yet, if rational investigation of mind is assumed to be like the excavation of a tunnel from opposite ends (a view which Arbib *et al.* seem to share), then each end must be set as the target of the other and hypothetical constructs should be tailored to allow interdisciplinary reduction.

Turning to nontheoretical considerations, the reader will find the book to contain many difficult, and several obscure, passages. Moreover, it is a pity that the architecture of the text is such as to require sustained strain and a lot of recursive reading. Yet the book fully deserves the reader's efforts which, in any case, are negligible compared with those made by the authors in producing such an enlightening, enriching and stimulating contribution.

EDOARDO BISIACH

**Cellular and Molecular Basis of Cholinergic Function.** Edited by M. J. Dowdall and J. N. Hawthorne. 1987. Pp. 941. Weinheim: VCH. Price DM 340.00.

Since the turn of the century when Dale made his fundamental discoveries on the muscarinic and nicotinic action of choline esters it was realized that acetylcholine was a key neurotransmitter in the CNS. This is quite evident from reading *Cellular and Molecular Basis of Cholinergic Function* which contains more than a hundred contributions on different aspects of the topic presented at the sixth international meeting in May 1986. In the introduction to this book Feldberg narrates his reminiscences of the thirties and gives insight into his pioneer work. Thus with Fessard he discovered the cholinergic nature of the neurons innervating the electric organ of Torpedo. Little could it be imagined at that time that this would become such a powerful tool for the study, not only of mechanisms of acetylcholine release but also for the discovery of the primary structure of the Torpedo nicotinic receptor. This fascinating work and the cloning of the responsible gene is described by Barnard and his colleagues in the second chapter. Recently the cDNA sequence of brain muscarinic receptor ($M_1$) has been reported The mechanisms of coupled receptor activation to cellular response is included in Part 1. Two stages can be identified—a rapid interaction of transmitter and receptor, then a slower second messenger transduction. There are accounts of the three systems—at the muscarinic receptor the integral membrane proteins (GTP-linked G proteins) interact with the well-known nucleotide cyclases (e.g., cyclic AMP) and the phosphoinositides involving protein kinase C. The next section of 34 chapters deals with the properties of cholinergic neurons. A great deal of impetus comes from work on the electric eel with its concentration of acetylcholine synapses in the electromotor system. This model is described in detail by several authors and contributions are made to the controversies covering the mechanism of release of acetylcholine The use of highly purified cholinergic vesicles has enabled the detailed composition of the cholinergic vesicle to be described (proteins include an ATP carrier; proton pump, actin, calmodulin-binding and proteoglycan components).

Section IId deals with trophic factors and regulatory molecules (adenosine, neuropeptides, etc.) and their effect on cholinergic neurons. Thus the remarkable discovery of NGF-responsive cholinergic neurons in the septal nucleus, diagonal band of Broca and the basal nucleus is reviewed by Thoenen and his colleagues. Unrelated to NGF is a hippocampal peptide which stimulates growth of septal neurons (Chapter 47). This type of research has potential relevance to the pathogenesis of neurodegenerative disease where the cholinergic system is frequently implicated (Chapters 75–78 and Alzheimer's disease, Chapters 98–104). The last part of the book also includes papers on neurotoxins, including botulinum, organophosphates and synthetic antagonists. There are several chapters on neuropharmacological topics and on diet, especially in relation to ageing.

The volume is well produced but a more extensive index would be of particular value when so many varied subjects are covered. It will be obvious that this is a specialist book for those interested in information covering a very broad range of research on the neurobiological aspects of the cholinergic system.

A. N. DAVISON

# ANNOUNCEMENTS

## Neurotraumatology Committee of the World Federation of Neurosurgical Societies

An award will be given for new research in neurotraumatology including basic or clinical studies involving trauma to the brain, spinal cord, or peripheral nerves This may include epidemiology as well as reports on progress on prevention, or a study of motor vehicle accidents, sport injuries, etc. Abstracts, in triplicate, are to be sent to the scientific programme committee of the 9th International Congress of World Federation Neurosurgical Societies by December 31, 1988. A full manuscript is subsequently required by the Chairman of the Committee of Neurotraumatology, Professor Robert P. Vigouroux, Department of Neurosurgery, C H U. Timone, 264 rue Saint-Pierre, 13385 Marseille Cedex 4, France, by February 28, 1989.

The winner of the award will be chosen by the Committee of Neurotraumatology of WFNS and presented by the Chairman of the Committee at the 9th International Congress.

## Second International Conference on the Pharmacology of Cerebral Ischaemia

This will be held at Marburg, FRG, on October 3–5, 1988, and will be convened by Professor J Krieglstein Sessions will include invited speakers, open oral and poster sessions on calcium antagonists, antagonists of excitatory amino acids, and other clinical and scientific sessions. For further details, contact Dr John Jennings, Medical and Scientific Conferences Ltd., The Studio, 12 High Street, Wheathampstead, Herts AL4 8AA, U.K.

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**Announcements** 768

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# CLINICAL CONCEPTS OF DUCHENNE MUSCULAR DYSTROPHY[1]

## THE IMPACT OF MOLECULAR GENETICS

*by* LEWIS P. ROWLAND

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## SUMMARY

Molecular genetics has transformed clinical concepts of Duchenne muscular dystrophy (DMD) in several different ways. (1) The disease can now be defined as a myopathy due to mutation at Xp21, a specific locus on the short arm of the X chromosome. (2) As a consequence of that discovery, any myopathy due to mutation at Xp21 should be a variant of DMD and should affect the same gene product. Moreover, any myopathy due to mutation at a location other than Xp21 should affect some other gene product. (3) For these reasons, DNA analysis is now needed for clinical diagnosis of muscle disease. (4) Xp21 myopathies may be mild or severe, may occur in females even though X-linked, and may be manifest only by high serum levels of creatine kinase. (5) Mental retardation is not consistently related to diseases that are encoded at Xp21. The association of mental retardation with DMD may be due to mutation in a separate gene near that for DMD. Concepts may soon be altered again as we learn about the affected gene product (dystrophin) and its role in these diseases.

## INTRODUCTION

There has not yet been time to assimilate the whirlwind of advances of molecular genetics. The publications accumulate so rapidly and in such numbers that the literature has been crowded by the technicalities, and by practical problems of carrier detection and prenatal diagnosis. Ethical problems and questions of gene therapy have also received attention, but little has been written about still another clinical revolution—concepts of heritable disease. Duchenne muscular dystrophy (DMD) provides a good example.

The issue can be stated directly. Until now, Duchenne dystrophy has been defined in clinical terms—pattern of inheritance, symptoms, signs on examination, changes on electromyography and muscle biopsy, and serum levels of sarcoplasmic

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enzymes. We must now add another criterion: evidence of a mutation at Xp21. DMD can be defined simply as a myopathy due to a mutation at Xp21. Two corollaries follow this definition (Rowland, 1987). First, any mypopathy due to mutation at Xp21 is a variant of DMD. (That view can be proven only by demonstrating that the same gene product is affected in each variant.) Secondly, any myopathy due to mutation at a locus other than Xp21 is likely to affect a gene product different from the one in Duchenne dystrophy (unless there is more than one subunit in the same gene product).

As a consequence of the change in definition, clinical concepts have also changed. (1) Already, DNA analysis is required for precise clinical diagnosis. Soon, we hope, there will also be tests for the gene product. (2) Although DMD is X-linked, Duchenne myopathies may occur in females. (3) DMD typically begins in infancy and the boys lose ability to walk by the age of 12 yrs. However, variant Duchenne myopathies may be much more benign. In patients of either sex, children or adults, weakness may begin later and is compatible with walking until late adult years. Becker muscular dystrophy (BMD) is an allelic variant of Duchenne dystrophy, not a separate disease due to change in a separate gene. (4) The minimal expression of the Duchenne gene is sometimes unexplained increase in serum levels of creatine kinase (CK) and other sarcoplasmic enzymes. In girls and women, this may be seen in obligate carriers; X,autosome translocations; or XO Turner syndromes. In boys and men, it may be seen in the McLeod syndrome. (5) It seems likely that mental retardation is not an expression of the Duchenne gene but is the result of a mutation in a separate neighbouring gene. (6) One direct result of the preceding changes is the erosion of the concept of limb-girdle muscular dystrophy. The remainder of this article is intended to provide the basis for those assertions.

## THE DUCHENNE GENE

### *The landmarks*

The search for the Duchenne gene may be said to have started with the paper by Botstein *et al.* (1980). They provided the theoretical basis for the use of restriction fragment length polymorphisms (RFLPs) to find genes for diseases of unknown gene product. Within 2 yrs, Murray *et al.* (1982) described the first DNA marker for the DMD gene. Soon there were two markers, with the important additional attribute that the sequences flanked the DMD locus (Davies *et al.*, 1983). That rapid progress was helped by the identification of DMD in girls with chromosome translocations that involved Xp21 (Greenstein *et al.*, 1977; Verellen *et al.*, 1978; Boyd and Buckle, 1986; Boyd *et al.*, 1987), denoting the general area of the DMD gene on the short arm of the X chromosome.

The saturation strategy then emerged. More and more RFLPs were added and it became practical to use the haplotype method for carrier detection and prenatal diagnosis, techniques that were in widespread use by the end of 1986 (Harper *et al.*, 1983; Bakker *et al.*, 1985; Hejtmancik *et al.*, 1986*a*, *b*; Darras *et al.*, 1987).

Two major hurdles remained. How would the gene itself be identified? And how would the gene product be identified?

Search for the gene was propelled when Francke *et al.* (1985) described a cytogenetic deletion of the region around Xp21 in a young man, B.B. That patient was also unfortunate enough to have 5 different X-linked disorders, including DMD. Kunkel and his associates (1985; Monaco *et al.*, 1985, 1986) then brilliantly used the technique of subtraction hybridization to identify the region of DNA that was missing in B.B., and that stretch of DNA must have included the gene for DMD.

### *Deletions in DMD*

The probes that emerged from the study of B.B. were used to study the deletions in other patients with DMD and BMD. That international project (Kunkel *et al.*, 1986*b*), a model of scientific co-operation, made it clear that the deleted areas covered an amazingly large span, and also that there was no relation between the size or location of the deletion and the severity of the clinical myopathy.

In the original study (Kunkel *et al.*, 1986), deletions were found in 5% of the cases but, as more probes were developed, the number of deletions has increased, perhaps to 50% (Robertson, 1987).

### *The Duchenne gene*

The probes were then used to walk the chromosome to find stretches of DNA that were found in different species, assuming that exons would be conserved in evolution. It was also assumed that the relevant gene product would be expressed in muscle. Both assumptions proved correct (Monaco *et al.*, 1986) and small exons were identified by hybridization to mRNA from muscle and heart. The gene or genes would have to cover 1,000,000 kb of DNA. The protein, if there were only one gene, would have a molecular weight of at least 500 kDa.

The international search for the Duchenne gene was funded in large part by voluntary health organizations, the Muscular Dystrophy Associations in the United States and Great Britain, as well as similar organizations in other countries. These organizations augmented the traditionally important governmental sources of research funds and provided the necessary flexibility in responding to novel avenues of investigation. As a result, the gene was identified in about 4 yrs.

### *The vulnerable crowd at Xp21; B.B., glycerol kinase and other neighbours*

The DNA of patient B.B. was an essential ingredient in the search for the DMD gene. In addition to DMD, B.B. had chronic granulomatous disease (CGD), retinitis pigmentosa, mental retardation, and the McLeod syndrome (lack of the Kell antigen in red blood cells, acanthocytosis, and high serum CK levels). The expression of 5 X-linked conditions by B.B. implied that genes for the other diseases were also located in or near the sequences deleted at Xp21.

As a by-product of the search for the DMD gene, the gene for CGD was identified by investigators in the laboratories of Kunkel and Orkin (Royer-Pokora *et al.*, 1986) and the gene for CGD took on a special place in history; it was the first gene to be isolated for a disease of unknown gene product. That achievement was the first example of what has been called 'reverse genetics' (Orkin, 1986); instead of using the affected protein gene product to find the gene, the DNA was identified before the gene product was known. The amino acid sequence of the CGD gene product was deduced from the sequence of bases in the cDNA; it proved to be a component of cytochrome b in granulocytes.

Another formerly obscure condition, glycerol kinase deficiency (GKD), also had clinical implications. That story started when Guggenheim *et al.* (1980) described 2 brothers with a syndrome of congenital adrenal hypoplasia (CAH), GKD, mental retardation, and a myopathy. The histological changes in muscle were similar to those of DMD, and the high serum level of CK were in the DMD range. At first, however, the authors did not think that the myopathy was DMD because there was no calf hypertrophy, and there was little symptomatic weakness (up to the age of 6 yrs). It seemed natural to believe that the myopathy was a consequence of the biochemical disorder resulting from the lack of GK. It soon became evident that lack of GK activity was not responsible for either the myopathy or adrenal insufficiency, because an equally severe lack of the enzyme was found in asymptomatic individuals (Rose and Haines, 1978; Wirth *et al.*, 1985). We might conclude that separate genes were involved in each of the major associated conditions (myopathy, GKD, and CAH).

That there were separate genes became evident as more families were identified and different combinations of clinical disorder were seen. Some families showed a tetrad of disorders: GKD, DMD, CAH, and mental retardation (von Petrykowski *et al.*, 1982; Reiner *et al.*, 1983; Dunger *et al.*, 1986; Saito *et al.*, 1986). Two brothers had CAH and DMD, but other conditions were not mentioned (Toyofuku *et al.*, 1981). Two families had GKD and symptomatic attacks of acidosis but none of the other disorders (Eriksson *et al.*, 1983; Ginns *et al.*, 1984); in one family, exercise intolerance was a possible manifestation of myopathy (Ginns *et al.*, 1984). One family had only GKD and CAH (Bartley *et al.*, 1982). Another family had CKD and CAH, with the addition of ornithine transcarbamylase deficiency (OTCD), but the child was too young to be evaluated for mental retardation (Hammond *et al.*, 1985). One severely retarded child with OTCD also had CGD but none of the other disorders (Francke, 1984).

The combinations of disorders associated with GKD seem to cover most of the possibilities and, although there have not yet been cases of OTCD with DMD, the gene for OTC has also been localized to Xp21. It therefore seems likely that the myopathy accompanying GKD is truly a form of DMD and that the clinical associations have depended on the pattern of deletion of neighbouring genes. In one family with the full tetrad of GKD, DMD, mental retardation and CAH, a deletion of Xp21 was demonstrated by DNA analysis and, only then (reversing the usual sequence), was a small cytogenetic deletion found in the middle of Xp21

(Wieringa *et al.*, 1985). A similar chromosome abnormality was later found in the mother of another patient (Saito *et al.*, 1986), and DNA deletions have been found without cytogenetic abnormality in 1 of 2 unrelated boys (Dunger *et al.*, 1986); the other case was attributed to a deletion of different size or position, or a rearrangement that led to inactivation of Xp21 genes. The last 2 cases were found by screening boys with DMD and testing the urine for glycerol.

Analysis of these and other deletions has provided a map of the sequence of the genes for the several disorders associated with GKD (Francke *et al.*, 1987; Seltzer and McCabe, 1987). B.B. and patients with GKD have also altered clinical concepts of DMD.

## TECHNOLOGY AND THE EVOLVING CONCEPT OF DUCHENNE DYSTROPHY

The definition of Duchenne dystrophy has changed with the technology of the times. The word 'dystrophy' was first used by Wilhelm Erb (1891). At that time, diseases were delineated in terms of postmortem pathology, and diseases of muscle were being separated from neurogenic diseases, but it must have been impossible for a clinician to have felt confident about making the distinction in a living patient.

It was not until the years after World War II that it became possible to make the distinction between neurogenic and myopathic disease by electromyography and the application of histochemical stains to muscle biopsy. The dystrophies were separated from other myopathies because they are, by definition, inherited. The X-linked pattern of DMD was established in the observations on Mormons made by Stephens and Tyler (1951) and by the pioneering studies of Walton and Nattrass (1954). Not all inherited myopathies, however, are termed 'dystrophies'. The dystrophies are separated from congenital myopathies and metabolic myopathies by three clinical criteria: (1) symptoms of a dystrophy are due to muscle weakness alone; (2) the weakness is progressive; and (3) there is no abnormal storage material in muscle.

The several forms of muscular dystrophy are separated on the basis of clinical features: age at onset; distribution of weakness; rate of progression; serum levels of CK and other enzymes; and patterns of inheritance. DMD is characterized by X-linkage, high serum CK from birth onwards, problems as soon as the boys begin to walk, and progression to wheelchair by the age of 12 yrs. Calf hypertrophy is common but not invariable. Becker, facioscapulohumeral, and limb-girdle types differ in essentials. Diagnosis has therefore depended on EMG, histochemistry and analysis of serum enzymes, in addition to the clinical features.

It is necessary now to add another criterion, one that depends on DNA analysis: evidence of mutation or deletion of Xp21. As a corollary, any myopathy with a mutation at Xp21 is allelic to, and therefore a form of, DMD; the same gene product should be affected, perhaps in different ways. Moreover, any myopathy that is assigned a locus at some other site is not a form of DMD. In time, identification of the gene product will be part of the definition.

There are also practical implications of the DNA criterion. For instance, we have seen a woman with an adult-onset myopathy; the differential diagnosis centred on limb-girdle muscular dystrophy and polymyositis. Years later, however, the patient's asymptomatic daughter gave birth to a son with typical DMD, stamping the propositus as a manifesting carrier. If appropriate DNA analysis had been available, the diagnosis could have been evident from the onset. For sporadic myopathies, diagnostic use of Xp21 probes is now just as necessary as EMG, muscle biopsy and serum CK determination.

The specificity of the Xp21 identification has been strengthened by the assignment of the Emery-Dreifuss muscular dystrophy (Boswinkel *et al.*, 1985), another X-linked dystrophy, and also an X-linked motor neuron disease (Fischbeck *et al.*, 1986) to different loci on the long arm of the X-chromosome, remote from Xp21. Emery-Dreifuss dystrophy therefore involves a gene that differs from the one for DMD and, presumably, a different gene product is also affected.

## CLINICAL PROBLEMS OF DUCHENNE DYSTROPHY

Even before DNA probes were developed, the diagnosis of DMD was regarded as accurate, and the condition was considered homogeneous. However, there has been lingering uncertainty about three problems—mental retardation, girls with DMD-like disorders, and the less severe X-linked myopathy, Becker dystrophy. Each of these problems has been illuminated by DNA analysis.

### *Mental retardation*

Among the original cases described by Duchenne, one of them was severely retarded and it has been estimated that about a third of the boys are educationally subnormal (Dubowitz, 1977). Emery *et al.* (1979) thought there might be two types of DMD; boys with mental retardation seemed to have later onset and walked longer than DMD boys with normal intelligence. However, unlike the muscle disease, the retardation is never progressive, and there is no consistent brain pathology. There are sometimes other retarded children in the family who do not have DMD, and some studies have failed to show any parallel between the presence of mental retardation and DMD (O'Brien *et al.*, 1983; Rabbi-Bortolini and Zatz, 1986*a*). Most important, linkage analysis with two probes has shown no evidence of heterogeneity in DMD that might be based on mental retardation (O'Brien *et al.*, 1983). There is, moreover, an inconstant relation of retardation to three other Xp21 syndromes: OTCD, GKD, and CAH. Since mental retardation does not invariably accompany lack of either ornithine transcarbamylase or glycerol kinase, the mental retardation so frequently seen with either biochemical disorder cannot be solely the result of the chemical derangement. The lack of consistent association also makes it unlikely that these biochemical disorders can account for the mental retardation of DMD. Instead, it seems most likely that there is a separate gene for mental retardation at Xp21, large enough to be seen occasionally with each of these syndromes—or with DMD.

### *Muscular dystrophy in girls and women*

Seventeen years ago, Penn *et al.* (1970) analysed the problem of DMD-like disorders in girls. Only 17 of 128 reported cases were regarded as possible variants of DMD, and none of the 17 had an affected brother or appropriate tests to exclude other neuromuscular diseases. That is, none was clearly DMD. Since then, DMD syndromes have been reported in females in the following situations.

1. Girls with X-autosome translocations have had myopathies that were sometimes mild and sometimes severe (Boyd and Buckle, 1986; Rabbi-Bortolini *et al.*, 1986*b*). The chromosome break in each case affected Xp21 but not always in precisely the same microsite (Boyd *et al.*, 1987). The normal X-chromosome seems to be preferentially inactivated in the lyonization process of the affected females with translocations; the Xp21 breakpoint in the translocated X then expresses the DMD mutation.

2. Girls or women with severe or mild myopathic limb weakness have been identified as obligate carriers by their positions in families with typical cases of DMD in boys (Zatz *et al.*, 1973; Moser and Emery, 1974; Meola *et al.*, 1981; Yoshioka, 1981; Olsen and Fenichel, 1982; Kaladhar Reddy *et al.*, 1984). There have also been 5 sets of identical twin sisters who were discordant for clinical myopathy; 4 of the 5 were obligate carriers (Chutkow *et al.*, 1987; Pena *et al.*, 1987; Younger *et al.*, 1987). Two sets of twins were analysed with DNA probes that proved monozygosity, but there were no evident deletions at Xp21. These cases are attributed to unequal lyonization, with inactivation of the normal X in the affected twin, leaving the X bearing the DMD mutation as the active X-chromosome in most muscle cells. Twinning seems to expedite this pattern.

3. A female could have a DMD-variant myopathy if she were also a manifesting carrier for DMD, GKD, CGD, CAD, or OTCD.

4. If there were no typical DMD cases or other Xp21 diseases in a family, myopathy in a girl or a woman could be identified as a DMD-variant only with DNA evidence of deletion of cytogenetic evidence of translocation. If there were no other cases in the family, and if there were no evidence of Xp21 deletion, it is not now possible to exclude a different, autosomal recessive, or 'limb-girdle' dystrophy (Gardner-Medwin and Johnston, 1984; Somer *et al.*, 1985; Marks *et al.*, 1986; Meola *et al.*, 1986; Yoshioka *et al.*, 1986).

### *Mild X-linked myopathy*

Becker muscular dystrophy is identical to DMD in all respects except for later onset and slower progression (Emery and Skinner, 1976; Ringer *et al.*, 1977; Mostacciuolo *et al.*, 1987). The conventional dividing line is use of a wheelchair by the age of 12 yrs for DMD, and after that time for BMD. Calf hypertrophy, serum CK values, distribution of weakness, and muscle histology are the same in the two conditions.

Analysis of DNA deletions (Kingston *et al.*, 1983; Fadda *et al.*, 1985; Hart *et al.*, 1987; Hodgson *et al.*, 1987; Monaco *et al.*, 1987) indicates that the Becker gene is the same as that for DMD or so closely aligned that the two cannot be distinguished. They cannot be distinguished by the chromosomal location of deletions within Xp21 or the size of the deletion. In fact, the two conditions seem to be allelic disorders.

There is tremendous variability in syndromes called BMD. Onset may be before the age of 5 yrs, or after 30. The individual may stop walking in adolescence or continue to walk after the age of 45 yrs. There are even families where one brother has typical severe DMD and the other has a benign disorder compatible with BMD (Furukawa and Peter, 1977; Hausmanowa-Petrusewicz and Borkowska, 1978; Mostacciuolo *et al.*, 1987; Spiegler *et al.*, 1987). That pattern, mild and severe cases in the same sibship, is difficult to explain if the conditions are allelic, but similarly unexplained variations are also seen in other heritable conditions; for instance, early and late, severe and mild forms in the same family are seen in hexosaminidase deficiency, acid maltase deficiency, or infantile and juvenile spinal muscular atrophy.

Females provide other evidence of the clinical variability of DMD variants. Obligate carriers may have no recognizable manifestations of the gene—or there may be only a high serum CK value, calf hypertrophy, or EMG abnormality, or there may be frank mild or severe limb weakness. In females, the severity of clinical manifestations might be affected by the relative activity of the paternal and maternal X-chromosomes, a balance determined by lyonization. However, similarly variable mild or severe patterns of myopathy have been reported with GKD, and it is not clear what determines severity of the myopathy in those cases.

### *McLeod syndrome and minimal expression of the Duchenne gene*

Just as high serum CK levels may be the only abnormal manifestation in an obligate carrier of the DMD gene, so an abnormal CK value may be the only manifestation of the DMD gene in men with the McLeod syndrome, one of the disorders of patient B.B. That condition was first described as a rare blood group by Allen *et al.* (1961), named after the patient. The basic disorder seems to be lack of a protein that serves as precursor of the Kell red blood cell antigen (Marsh, 1978; Marsh and Redman, 1987); the erythrocyte membrane is altered producing the abnormally-shaped cells, acanthocytes.

High CK values seem to be an invariant part of the syndrome, although the patients have no symptomatic limb weakness and there is little necrosis in the muscle biopsy (Marsh *et al.*, 1981; Zyskowski *et al.*, 1983). The patients are usually asymptomatic men, discovered when they volunteer to be blood donors.

The McLeod syndrome is inherited in X-linked fashion and a relationship to DMD was suggested by Swash *et al.* (1983). When the case of B.B. was reported in 1985, it was known that the chromosomal location of McLeod was likely to be Xp21—and there had already been reports of chronic granulomatous disease with either the McLeod syndrome (Marsh, 1978) or with DMD (Kousseff, 1981).

If the McLeod syndrome maps to Xp21, then 'idiopathic hyperCKaemia' (Rowland *et al.*, 1980; Schwarz *et al.*, 1984; Sunohara *et al.*, 1984) may sometimes be the minimal expression of the DMD gene—high serum CK levels in individuals who have no symptoms of limb weakness and, sometimes, no evidence of myopathy in EMG or muscle biopsy. In the future, the diagnosis of 'idiopathic hyperCKaemia' should be made only after appropriate study of the Kell antigen.

If an abnormally high serum CK level, as in the McLeod syndrome, is a manifestation of the DMD gene, that might shed light on two other mysteries—why some, but not all, people who are susceptible to malignant hyperthermia have persistently high serum CK values, and why patients with DMD may be more susceptible than normals to anaesthetic reactions that include myoglobinuria (Rowland, 1984). Naturally, this is not the only cause of unexplained high serum CK levels which, for instance, may be an asymptomatic prelude to distal myopathy (Galassi *et al.*, 1987). Also, slightly high CK values may accompany the syndrome of acanthocytosis and movement disorders (Spencer *et al.*, 1987), a condition that is not apparently X-linked.

This view of mild, even asymptomatic, myopathy as an expression of the DMD gene conforms to the opinions of Worton (Dubowitz and Worton, 1986) and differs from the view that BMD and DMD may be separate disorders. It also differs from the view that apparent recombination of Xp21 restriction fragments in a boy implies a different disease, one that may be autosomal recessive (Fischbeck *et al.*, 1987), whether the myopathy is mild or clinically typical of DMD. That hypothesis may not be necessary because the number of deletions found at Xp21 seems to depend on the number of informative probes available. Moreover, it seems reasonable to hope that it will ultimately be possible to detect mutations other than frank deletions.

## IDENTIFYING THE GENE PRODUCT

The year 1987 was a crucial one in the history of DMD, in particular—and human genetics, in general. The crowning achievement was set forth in a prodigious series of papers from the laboratory of Louis Kunkel, culminating in the identification of the DMD gene-product as a new protein, one they called dystrophin. But there was one more by-path to be circumvented early in the year. The power of molecular genetics was used to terminate the last of the 'fishing expedition' approaches to identify the gene product. That is, 'logic' had been used for many years to suggest this or that hypothesis about possible candidates for the crucial protein.

At an international meeting in October 1986, Monaco *et al.* (1986) presented their data about the broad expanse of the DMD exons. At the meeting, Donald

Wood indicated that there were 2 muscle proteins that might be related to a gene that large. One was titin (about 1,000,000 Da) and the other was nebulin (about 500,000 Da). At the Columbia-Presbyterian Medical Center, Eduardo Bonilla's electron micrographs of DMD muscle suggested that there was disruption of the I-band where nebulin was thought to be located, and gel electrophoresis showed that nebulin was absent or much reduced in content in all DMD muscle samples studied (Wood *et al.*, 1987; M. Zeviani *et al.*, 1988). The results were consistent with the hypothesis that nebulin is normally involved in maintaining the alignment of muscle filaments and, therefore, in generating tension (Horowitz *et al.*, 1986). Also, lack of nebulin might explain some earlier data of Wood *et al.* (1978) indicating that skinned muscle fibres from DMD patients did not generate tension normally. Within a few months, however, the development and application of antibodies to nebulin showed that nebulin was not totally absent in DMD muscle (Sugita *et al.*, 1987; Furst *et al.*, 1987), and immunocytochemical studies showed that nebulin was still present in sections of DMD muscle (Furst *et al.*, 1987; Bonilla *et al.*, 1988).

The final blow to the candidacy of nebulin was the development of DNA probes to nebulin in the laboratories of Eric Schon at Columbia-Presbyterian and Roy Schmickel at the University of Pennsylvania, providing evidence that the gene for nebulin is on human chromosome 2, not the X-chromosome (H. Stedman, J. Sylvester and R. Schmickel, unpublished). Nebulin was therefore eliminated as a candidate for the gene product of an X-linked disease. Nevertheless, the amount of nebulin seemed to be much decreased in several studies of DMD muscle (Wood *et al.*, 1987; Medori *et al.*, 1987; Sugita *et al.*, 1987; Hoffman *et al.*, 1988). It is not known why the amount of nebulin should be so low, or whether the paucity of nebulin has any functional consequences.

By the end of 1987, Kunkel, Hoffman, Monaco and their associates at Harvard had published a towering series of historic papers. They found that the gene for dystrophin was highly conserved in mice and humans (Hoffman *et al.*, 1987*c*) and that the organization of DNA was similar in the region of the gene in mice and humans (Chamberlain *et al.*, 1987); more than 90% of the DNA sequence was identical. They then used the mouse cDNA to produce large segments of the protein in *E. coli*. They used the protein so produced to make antibodies, and the antibodies as reagents to identify the protein in electrophoresis gels, and to purify the protein.

This was a triumph of 'reverse genetics', isolating the gene first and then employing the DNA to identify the gene product. With the antibodies, they found that dystrophin was absent or less than 3% of the normal abundance in 95% of the boys clinically diagnosed as having DMD; the protein was usually present in Becker cases in normal amounts but of abnormal size (Hoffman *et al.*, 1988). They found that open reading frames were interrupted in DMD to truncate the product, but that residual protein of altered form (and presumably incomplete function) was still present in BMD (Hoffman *et al.*, 1988). There were some inconsistencies between the clinical phenotype and the 'dystrophin' phenotype, especially in Becker cases (Hoffman *et al.*, 1988). They found that dystrophin was also missing in an X-linked myopathy of mice, the *mdx* mouse (Hoffman *et al.*, 1987*b*).

Identification of the gene product that is affected in DMD, BMD and the *mdx* mouse opens a new phase in research related to muscular dystrophy, a new phase in which there is much to be done. The normal function of dystrophin is not known and will have to be elucidated. It will be necessary to understand how the lack of dystrophin is compatible with some development and function of muscle in young children with DMD and, by definition, in all patients with BMD. It will be necessary to understand how lack of dystrophin causes the manifestations of DMD: limb weakness, progression of weakness for more than a decade, high serum levels of CK for years, and progressive fibre degeneration of muscle with replacement by fat and connective tissue. It will be essential to understand the few (but important) inconsistencies between clinical and dystrophin phenotypes in patients with either BMD or DMD, to determine how both DMD and BMD phenotypes can ever occur in the same family, and how the several different Xp21 myopathies are related.

After years of wishful thinking, investigators now seem to have been provided with a true animal model of DMD, so that new approaches can be applied. However, the *mdx* mice show little evidence of limb weakness and it will be necessary to determine why lack of the protein in the mouse causes so little functional disability. Finally, it remains to be determined whether knowledge of the gene product can lead the way to a rational and effective therapy.

These are formidable problems, but the astounding progress of the past few years gives hope that these new problems can also be resolved. The power of recombinant DNA methods and the spirit of international scientific cooperation that have been applied to the Duchenne gene are not yet exhausted, and we know not what new methods are yet to come. The pace of advance is accelerating; the next decade of muscular dystrophy research is likely to be even more exciting than the last one.

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# CHANGES IN STRATEGY OF AIMING TASKS IN PARKINSON'S DISEASE

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## SUMMARY

Fundamental differences in bradykinesia in parkinsonian patients and nonparkinsonian elderly subjects were analysed. Our method was an aiming task in which the coordination of eye and hand movements was measured when the subject attempted to catch up with a visual target.

The coordinated eye and hand movements started towards the target almost simultaneously in the normal subjects when the target was in the periphery of the visual area. The initial abnormality in parkinsonian patients was an isolated delay of coordinated hand movement. In the typical bradykinetic patients, the hand movement did not start while the target was still in the peripheral visual area but only when the image of the target was near or on the fovea. The aiming tasks were then performed step by step following visual confirmation. Thus patients with typical bradykinesia showed a failure of ballistic hand movement preprogrammed to the visual target in the peripheral visual area, and the strategy of coordination was changed. In contrast, the disturbance of the ballistic hand movement in the nonparkinsonian elderly subjects had no consistent strategy for coordination of the visually guided eye and hand movements.

## INTRODUCTION

The examination of coordinated eye and hand movement is applicable to physiological analysis of bradykinesia in parkinsonian patients (Warabi *et al.*, 1986*b*). In this study we attempted to show the fundamental difference of motor programs between parkinsonian patients and nonparkinsonian elderly subjects in performing a visually guided task.

The understanding of bradykinesia has been advanced through the analysis of visually guided hand movement (Flowers, 1975, 1976; Angel *et al.*, 1970; Warabi *et al.*, 1986*b*). However, parkinsonian patients are not easily differentiated from elderly subjects with regard to their reaction times and duration times of movement (Evarts *et al.*, 1981). Moreover, ballistic hand movement is disturbed not only in parkinsonian patients but also in elderly subjects, as we demonstrate in this paper.

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In a preceding paper (Warabi *et al.*, 1986*b*) we described the abnormalities occurring in the coordination of eye and hand movement in the early stage of Parkinson's disease. In the present study, we mainly analysed parkinsonian patients with typical bradykinesia with special reference to the time sequence of eye and hand movements in visually guided tasks. The results obtained suggest that the bradykinesia may be associated with reorganization of motor function in parkinsonian patients.

## SUBJECTS AND METHODS

### *Healthy subjects*

Fifteen volunteers aged 60–86 yrs were studied. One group consisted of 8 subjects aged under 70 yrs (mean 62.5), the other 7 elderly subjects over 70 yrs (mean 79.5) being chosen because they showed multisaccadic eye movements in over 20% of tasks. (Multisaccadic eye movement was seen frequently in 33% of elderly subjects over 70, but was also seen uncommonly in those under 70 (Warabi *et al.*, 1984).) None of the subjects in either group had a history of neurological (including extrapyramidal) or mental disorder, and all of them had good visual acuity (better than 20/40) with or without correction.

### *Parkinsonian patients*

Thirty-one volunteers were selected from patients with Parkinson's disease. They were informed of the purpose and procedures of the experiment, to which they gave their consent. The criteria for subject selection were (1) a primary symptom of bradykinesia, with other symptoms, such as tremor or rigidity, being relatively mild; (2) no signs of obvious mental disorder or complaints of vertigo or visual disturbance; (3) uncorrected binocular visual acuity of 20/40 or better.

The parkinsonian patients were classified into 4 groups, essentially following the grading of Hoehn and Yahr (1967): I, mild; II, moderate; III, severe; IV, very severe. I to III correspond to Hoehn and Yahr's grades, while IV in our study included patients with Hoehn and Yahr's grades IV and V. Seven patients (3 with grade III, 4 with grade IV) who were characterized by multisaccadic eye movement (occurring in more than 20% of saccades) were considered to have an advanced degree of bradykinesia (Owen *et al.*, 1983; Warabi *et al.*, 1986*b*). Two akinetic patients (grade IV) differed from the other 5 in that their reaction times and duration times of hand movement were extraordinarily long and most of their eye movements were multisaccadic. They were classified as having very severe bradykinesia in the results (parkinsonian-akinetic in the Table), and the other 5 as having typical bradykinesia (parkinsonian-M-saccade in the Table).

## PROCEDURE

The details of the procedures of the experiment and of the methods of data analysis have been described in previous papers (Warabi *et al.*, 1986*a*,*b*) and are only summarized here. The subject was asked to follow the displacement of the target with a laser-beam spot operated by hand flexion and extension as quickly and accurately as possible. The visual target was a series of 7 light-emitting diodes (LEDs), red and vertically rectangular, placed in a horizontal plane at 10° intervals. The 7 LEDs were lighted one at a time; at irregular intervals as each was extinguished, it was replaced simultaneously by another LED. Target displacements of 10,20,30, and 40° to either right or left were randomly executed. Ten executions were averaged for each target displacement.

Two experimental paradigms were used. In the first, the subject was asked to follow a target with the laser spot; in the second, the target LED was extinguished for 1 s immediately after the onset of a saccadic eye movement. Eye movement was recorded with silver-silver chloride electrodes attached to the forehead and to the inner and outer canthi of the right eye. Wrist flexion and extension movements were recorded by displacement of the target tracker with a potentiometer simultaneously with the electro-oculograms. The gain in open-loop hand movement was defined and measured as the amplitude of the initial quick hand movement during the blackout period divided by the amplitude of the target displacement. The data were stored on magnetic tape and displayed later on either a pen oscillograph or a digital memory scope (Nihon Koden RAT 1100 and NEC San-Ei 7S07).

## RESULTS

### *Coordinated eye and hand movements in normal elderly subjects*

The response in the aiming task in the present study was a ballistic hand movement occurring shortly after a saccadic eye movement in following the target (fig. 1A). Both the eye and hand movements consisted of an initial ballistic movement and subsequent correcting movements. Results for 20° displacements are listed in the Table. In the group of subjects aged less than 70 yrs, the oculomanual onset latency was $41 \pm 22$ ms (mean ± SD) and the open-loop gain was $0.95 \pm 0.07$ (mean ± SD) (*see* Table). Both of these were comparable to those of normal young subjects (Warabi *et al.*, 1986*a*). However, the reaction time in both eye and hand movements was prolonged in elderly subjects (*see* Table) in comparison with values for young subjects, described in a preceding paper (Warabi *et al.*, 1986*a*). The multisaccadic eye movement was observed frequently in subjects aged over 70 yrs but not in those under 70.

### *Coordination in elderly subjects with multisaccades*

The aiming tasks of subjects in the second control group were characterized by multisaccadic eye movements and slow visually guided hand movements (fig. 1B). The average occurrence of multisaccadic eye movement was 35.2% in the aiming tasks executed by these subjects. The reaction times of the eye as well as of the hand movement were long, and the oculomanual onset latencies were mostly variable and inconsistent (*see* Table). Furthermore, hand movement occasionally started before the onset of eye movement. The open-loop gain of the ballistic hand movement varied from 1.2 to $< 0.2$. Thus the eye and hand movements in elderly subjects with multisaccadic eye movement seemed to be initiated without any consistent coordination between the two movements for achieving the visually guided aiming task.

### *Coordination in parkinsonian patients with typical bradykinesia (grades III and IV)*

In the early stage of Parkinson's disease, multisaccadic eye movement was rarely seen, and the sequences of the eye and hand movements were normal (fig. 2A). However, in the patients with typical bradykinesia, multisaccadic eye movement occurred frequently and oculomanual onset latency was markedly prolonged (*see* Table). We analysed the visually guided eye and hand movements in 5 typical bradykinetic patients with multisaccadic eye movement. The average occurrence of such eye movement in these patients was 41.3%. The reaction time of eye and hand

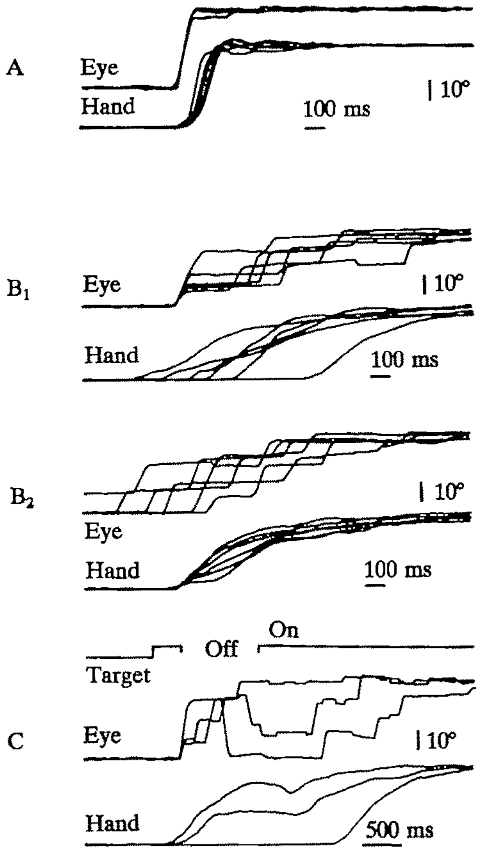

FIG. 1 Motor responses of eyes and hands of elderly normal subjects. Six or 3 responses to 40° target displacements are superimposed. A, eye and hand movements of a 65-year-old normal subject. The motor responses have been superimposed, adjusting the sweeps with respect to the onset of saccadic eye movement. A saccadic eye movement was followed by a hand movement with a short constant oculomanual onset latency of approximately 45 ms. The eye movement consisted of an initial saccade and a subsequent correcting saccade. In the majority of cases, the error-correcting saccadic eye movement occurred only once before the target image was located on the fovea. The amplitude of the correcting saccade was approximately 10% of the target angle. The onset of hand movement was slightly delayed after the saccade The hand movement also showed initial and correcting movements. The initial movement was large enough to reach the target and was frequently associated with an overshoot or an undershoot. The correcting movement showed various forms, such as a stepped procedure or a slow smooth movement. The eyes were fixed on the target throughout the period of hand movement. B, eye and hand movements of a 78-year-old normal subject with multisaccadic eye movement. B$_1$, the motor responses have been superimposed, aligning them with the onset of saccadic eye movement. The target with a 40° angle was located by multisaccadic eye movement. The onset of hand movement was not consistent with the onset of eye movement and occasionally occurred before the onset of saccadic eye movement. The hand movement was slow and the duration was long (mean duration of hand movement: 1543 ms, SD 417 ms). B$_2$, same responses as B$_1$, but the sweeps have been rearranged with respect to the onset of hand movement instead of the onset of eye movement. The oculomanual latencies showed large variations and that there was no obvious correlation between the onset of the eye and hand movements. C, aiming tasks in the second paradigm of the same patient as in B. The target light was turned off as soon as the saccade toward the target was initiated. The target was invisible during the time when the eyes were directed towards the target position. The single or multisaccadic eye movements occurred towards the target position, while the open-loop hand movement took place in the dark towards the target, which can be seen in the two traces in the figure. However, in the other trial, the hand movement did not start until the target was reilluminated. The average open-loop gain of this elderly subject was 0.68 (SD 0.37).

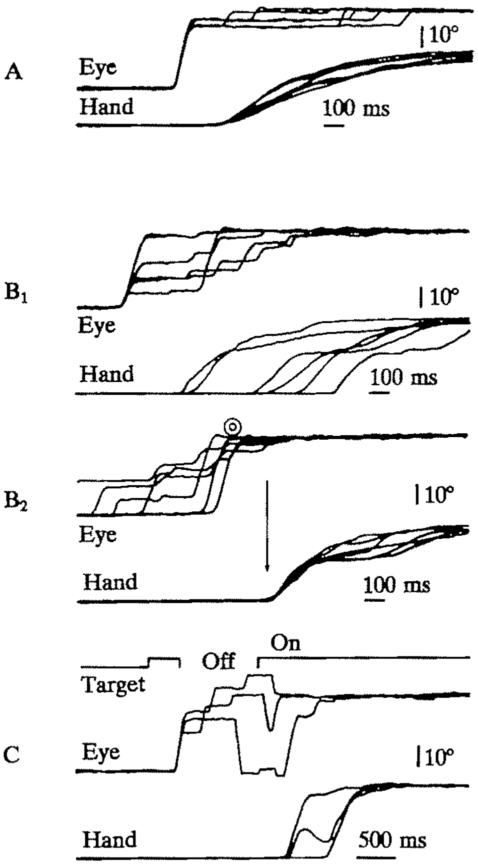

FIG. 2. Motor responses of parkinsonian patients. Six or 3 records are superimposed for 40° target displacements. A, parkinsonian patient (grade II) The motor responses have been superimposed, aligning them with the onsets of saccadic eye movement with constant latency A saccadic eye movement was followed by a slow hand movement. The eye movement consisted of an initial saccade and a subsequent correcting saccade with a fairly long latency. The onset of hand movement was time-locked to the onset of the saccade. The average oculomanual onset latency was 142 ms. B, motor responses in a parkinsonian patient (grade III) with multisaccadic eye movements. $B_1$, the motor responses have been superimposed, aligning them with the onset of saccadic eye movements. The target angle was 40°. The target image was located on the fovea by multisaccadic eye movement. The oculomanual onset latency showed large variations. $B_2$, the same motor responses as $B_1$ but the sweeps have been rearranged with respect to the onset of hand movement. The onset of hand movement has a closer temporal relationship with the end of the eye movement (indicated by the double circle). The end of the eye movement corresponds to the beginning of fixation. During this period, the target image is maintained on the fovea. The interval between the onset of fixation and the onset of the hand movement was approximately 180 ms. C, 3 motor responses to the second paradigm in the same patient as in B have been superimposed with respect to the onset of saccadic eye movements. The target light was turned off as soon as the saccade was initiated. The target was invisible when the eyes were directed towards the target position and the visual processing by the fovea was disrupted. No open-loop hand movement took place during the black-out of the visual target. However, after the saccade had located the reilluminated target image on the fovea, the visually guided hand movement started towards the target. Therefore, the hand movement was selectively generated by the visual information dependent on the foveal mechanism. In patients with advanced parkinsonism showing multisaccadic eye movement, the peripheral visual stimulation is thus unavailable for initiating visually guided hand movements

movements and oculomanual onset latency in grades III and IV were longer than those in grades I and II. The open-loop gain of the ballistic hand movements was markedly decreased (*see* Table).

The most remarkable change in the patients with typical bradykinesia was in the temporal sequence of the eye and hand movements. In the normal subjects and grades I and II bradykinetic patients, the onset of hand movement was closely related to the onset of the saccadic eye movement (fig. 2A). In contrast, the onset of hand movement was more closely related to the end of the eye movement in the patients with advanced bradykinesia (figs 2B, 3B). The image had already reached a point near or on the fovea at the onset of hand movement, so that at the onset of hand movement the simultaneous eye position was 19.6° towards the 20° target angle (Table). Moreover, in the second paradigm, when the target light was extinguished for 1 s immediately after the onset of saccadic eye movement, the hand movement did not start while the target was still in the peripheral visual area but only when the target image had reached a position near or on the fovea (fig. 2C). Thus in patients with typical bradykinesia hand movement started only after the target image had reached the fovea as a result of the eye movement.

TABLE. DATA FOR VISUALLY GUIDED EYE AND HAND MOVEMENTS (TARGET ANGLE 20°)

| *Group* | *n* | *Age (yrs) Mean* | *Frequency. of multisaccade (%) Mean* | *Reaction time of eye mvt (ms) Mean (SD)* | *Reaction time of hand mvt (ms) Mean (SD)* | *Duration of hand movement (ms) Mean (SD)* | *Oculomanual latency (ms) Mean (SD)* | *Eye position at onset of hand mvt (deg) Mean (SD)* | *Open-loop gain of hand mvt Mean (SD)* |
|---|---|---|---|---|---|---|---|---|---|
| Normal | 8 | 62.5 | 8.8 | 388(57) | 429(55) | 949(93) | 41(22) | 7.9(2.6) | 0.95(0.07) |
| Normal M-saccade | 7 | 79.5 | 35.2 | 513(113) | 729(153) | 1365(350) | 216(170) | 12.0(4.0) | 0.53(0.08) |
| Parkinsonian grade I | 11 | 55.7 | 3.3 | 354(41) | 451(64) | 1161(337) | 93(26) | 14.4(2.4) | 0.83(0.09) |
| Parkinsonian grade II | 10 | 60.2 | 7.1 | 394(88) | 549(89) | 1339(380) | 153(27) | 18.5(0.8) | 0.67(0.14) |
| Parkinsonian grade III | 3 | 67.7 | 7.8 | 450(60) | 659(81) | 1495(166) | 220(44) | 18.3(0.1) | 0.50(0.10) |
| Parkinsonian M-saccade | 5 | 76.2 | 41.3 | 839(100) | 1062(224) | 1729(245) | 363(94) | 19.6(0.3) | 0.08(0.06) |
| Parkinsonian (akinetic) | 2 | 78.0 | 74.5 | 1344(748) | 2105(933) | 4359(443) | 661(85) | 19.7(0.3) | < 0.02 |

The frequency of multisaccadic eye movement in the total trials of the aiming tasks, the reaction times of hand and eye movement, the duration of the hand movement, the oculomanual onset latency, the simultaneous eye position at the onset of the hand movement, and the open-loop gain of the hand movement of the visually guided aiming task to the target at a 20° angle are listed for the normal elderly subjects and for the parkinsonian patients with different grades of disability. Ten trials in each subject were averaged and the mean (SD) was calculated for each group. Mean = group mean; SD = standard deviation; normal M-saccade = the second group of normal elderly subjects with frequent multisaccadic eye movement; parkinsonian M-saccade = typical bradykinetic patients with multisaccadic eye movement.

### *Eye and hand movements in parkinsonian patients with very severe bradykinesia (grade IV)*

The bradykinesia was very severe in the 2 grade IV patients. They could scarcely stand and carried out the visually guided hand movement only with the greatest difficulty. The latency of hand movement was extraordinarily long, and the movement itself occurred gradually and very slowly. The frequency of multi-saccadic eye movement in these 2 patients when following the targets was the highest among all the subjects in this study. Oculomanual onset latency was very long and quite variable. The open-loop gain of hand movement was constantly near zero (Table).

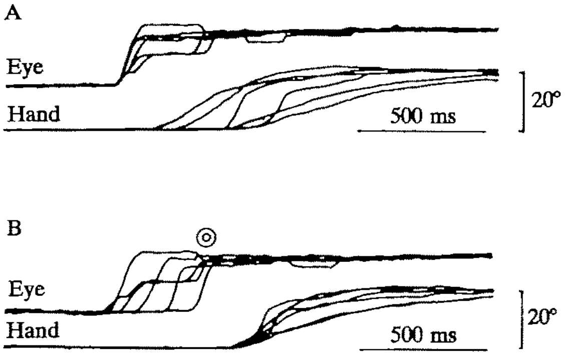

FIG. 3. Eye and hand movement recordings from a further parkinsonian patient (grade III) with typical bradykinesia (parkinsonian M-saccade in the Table). The angle of target displacement was 20°. The responses have been superimposed by aligning them with the onset of saccadic eye movement (A) and by rearranging the same responses with respect to the onsets of hand movement (B). A close temporal correlation was observed between the end of the eye movements (double circle) and the onset of the hand movements in B

## DISCUSSION

The motor responses requiring both the eye and hand movement systems involve two steps of motor performance which respectively depend on two different types of retinal function (Warabi *et al.*, 1986*a*). One step is the peripheral mechanism which measures the approximate distance between the target and the fovea. Then the saccadic eye movement and hand movement place the image of the target and the tracking marker near or on the fovea where visual acuity is best. The other step is the foveal mechanism which recognizes the positional error of the target and the tracking marker relative to the fovea. The tracking marker can then be corrected and stabilized on the target.

The open-loop gain is preprogrammed for the target in both the ballistic eye and hand movement, which depend on the peripheral retinal mechanism (Young and Stark, 1963; Miles and Evarts, 1979; Polit and Bizzi, 1979). However, the motor systems of eye and hand movement are controlled by independent neural mechanisms. Interestingly, only the motor system of the ballistic hand movement is disturbed in the early stages of Parkinson's disease. Prolongation of the oculomanual onset latency occurs first (Warabi *et al.*, 1986*b*). Finally, patients with advanced bradykinesia fail to catch up with the target in the peripheral visual field in the ballistic hand movement. Our results indicate that the coordination between the eye and hand movement is reorganized so as to locate the visual target more reliably: hand movement starts toward the visual target only after it has been located on the fovea through the saccadic eye movement. Characteristically, this new strategy for the coordination of the eye and hand movements is observed only in advanced and typical bradykinetic patients, whose eye movements are usually distinguished by the presence of multisaccades. The special quality of this new strategy is that the patient has to perform the aiming tasks step by step after locating the target, by means of the saccade, on the fovea where visual acuity is best. Therefore, when the visual target or the tracking marker accidentally slips from the subject's view, the target or the tracking marker has to be relocated by eye movement followed by recorrection of hand position. The multisaccadic eye movement also requires more time to locate the target and delays the onset time of hand movement. Thus it can be assumed that the characteristic symptoms of bradykinesia are produced not only by the longer reaction time and duration of movement, but also by the new strategy for the coordination of eye and hand movements.

Our observations indicate that the strategy coordinating eye and hand movements operates until the late stage of Parkinson's disease. Since measurement of the target position, which must be converted into the appropriate amplitude of eye movement, is possible in parkinsonian patients (White *et al.*, 1983; Warabi *et al.*, 1986*b*), reorganization of motor functions may take place in order to accomplish purposeful eye and hand movement. It is also thought that the extent of the disturbances in the open-loop system is not uniform among the different motor systems, and that the unaffected motor system is probably able to compensate for the affected motor system in parkinsonian patients. In the most advanced stage of bradykinesia, however, patients failed to show any steady temporal correlation between the start of both eye and hand movements, suggesting that the open loop system and available strategy for the coordination between the eye and hand motor systems totally fail to function in these akinetic patients.

In contrast to parkinsonian patients, elderly normal subjects, whose aiming tasks are also characterized both by multisaccadic eye movement and abnormal ballistic hand movement, had no consistent coordinated eye and hand movements. The visually guided hand movements of these elderly subjects were usually slow but clearly different from the bradykinesia of parkinsonian patients.

One effect of ageing is an impairment of the sensory process which provides the necessary information for individual motor functions (Warabi *et al.*, 1986*a*). Subsequently, the execution of an appropriate motor response seems difficult for elderly subjects because of the inappropriate measurement of the target position which must also be converted into the amplitude of the eye and hand movement. Thus we considered that a new strategy for the coordination of eye and hand movements is unavailable to these elderly subjects.

Multisaccadic eye movement was a common feature in both the elderly subjects and parkinsonian patients, and it is suggested that these multisaccades are produced by the impairment of either the sensory or motor process. However, it is notable that these different forms of impairment in the sensorimotor process involved in the aiming task characterize the different types of slowness in elderly normal subjects and parkinsonian patients.

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# ACUTE PSEUDOBULBAR MUTISM DUE TO DISCRETE BILATERAL CAPSULAR INFARCTION IN THE TERRITORY OF THE ANTERIOR CHOROIDAL ARTERY

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## SUMMARY

Pseudobulbar mutism is rarely attributed to bilateral discrete posterior limb internal capsule-medial globus pallidus infarction. Few cases of bilateral anterior choroidal (AchA) artery territory infarction have been reported. We present 8 patients with ischaemic stroke in this location and vascular distribution who have a characterizable syndrome. All had the abrupt onset of inability to speak, swallow or phonate, accompanied by varying degrees of facial diplegia, hemiparesis, hemisensory loss, lethargy, neglect and change in affect. The appearance of clinical signs depends upon the presence of a new infarct contralateral to an older lesion in mirror position. The pathogenesis and progression of neurological deficit appears to be intimately related to hypertension. The role of intrinsic intracranial vascular pathology related to diabetes mellitus, embolism of cardiac origin and atherosclerosis is currently undefined. The prognosis for recovery is poor. Half of our patients died within a year of onset of symptoms. Capsular pseudobulbar mutism is recognized by the abrupt appearance of neurological deficit consistent with internal capsular pathology and is confirmed by CT scan or MRI.

## INTRODUCTION

Acute mutism with pseudobulbar palsy due to discrete bilateral internal capsule infarction is rare. Reports bearing this clinical-anatomical correlation have emphasized interruption of the corticobulbar tract at the capsular genu as the locus of pathology. We now highlight the pertinent features of 8 cases of acute pseudobulbar paralysis with a severe degree of speech loss due to ischaemic stroke. Infarction in these patients was localized by CT scanning and MRI to the posterior two-thirds of the posterior limb of the internal capsule and adjacent medial globus pallidus, in the territory supplied by the anterior choroidal artery (AchA).

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## CASE REPORTS

### *Case 1*

This 61-yr-old right-handed woman had a 10 yr history of hypertension and 45 yrs of heavy smoking. For 6 months before admission, she had had intermittent bowel and bladder urgency. One month before, she had developed weakness in her right arm and leg with slurred speech. These symptoms improved but she was left with burning pain in the leg. In addition, she complained of intermittent blurring of vision of both eyes. On admission, the blood pressure was 190/100 mmHg; the heart rate was regular, 70/min. She was alert and orientated. Arteriovenous nipping was prominent on fundoscopy The pupils and eye movements were normal. She had a depressed corneal reflex and facial perception of pin-prick on the right. The right half of the soft palate did not elevate on phonation. The right arm and leg were moderately weak and ataxic. She used a cane in order to walk. Pin-prick and touch sensation on the right was decreased. The tendon reflexes were bilaterally brisk, more so on the right, and there were bilateral extensor plantar responses.

Two days after admission the patient complained of new left-sided weakness and increased slurring of speech, the weakness progressing that day to hemiplegia. The next day urinary retention was present and over the following weeks intermittent catheterization was required. She regained strength in the left arm, but the left leg remained paralysed. Intermittently during this time, despite medication, her blood pressure was raised, at times up to 210/120 mmHg. Suddenly, 6 weeks after admission, the patient was found lethargic with a blood pressure of 240/120 mmHg. On examination she was cooperative. There was a left head and eye gaze preference as well as right-sided auditory neglect. She was unable to move her eyes past the midline to the right. The oculocephalic reflex was intact. The pupils were normal, the right corneal reflex absent and there was severe facial diplegia, eye closure equally weak to mouth movement. Her gag reflex was absent, the palate hung low in the back of the throat, and she was unable to swallow, phonate or protrude her tongue. Tongue movement was slowed and limited in range. She could not approximate her lips. The right-sided hemiparesis had now become complete. Bilateral extensor plantar responses, left leg paralysis, hyperreflexia and sensory findings were unchanged. A CT scan showed periventricular lucencies and a discrete right-sided lucency in the middle third of the posterior limb of the internal capsule. Repeat CT scan and MRI 1 week later showed evolution of the right lucency and a new lucent area in mirror position on the left. Both lucencies now extended superiorly into the caudate nucleus immediately lateral to the lateral ventricle and adjacent white matter (fig. 1). Other laboratory results are summarized in Tables 1–3.

A gastrostomy was performed because of persistent dysphagia. Two months after admission, the left leg remained paralysed and the other limbs were mildly paretic. Her pseudobulbar paralysis remained severe. Her speech had slightly improved but was limited to severely distorted single words. Her voice was breathy, low pitched, monotonous and hypernasal. Although intermittently lethargic, she could now communicate with the help of an alphabet pointing board and by nodding 'yes' and 'no'. She was discharged to a nursing home and 1 year later was still alive.

### *Case 2*

This 68-yr-old right-handed man developed sudden numbness of the left leg one evening. During the night, his wife noted that he had unintelligible speech and marked weakness of the right face and leg. The following morning he could not stand. He had a 7 yr history of untreated hypertension. He had had several strokes, causing repeated weakness of the right limbs, minimal slurring of speech and mild dysphagia, bowel and bladder incontinence and depression.

On admission, blood pressure was 160/100 mmHg, the pulse was 96/min and regular. He was alert but mute. Pupillary reactions and eye movements were normal. There was right-sided face weakness, affecting the upper and lower face, the gag reflex was depressed and the tongue deviated to the right. There was spastic paralysis of the right arm. There was moderate weakness of the right leg, mild left arm and leg weakness, bilateral hyperreflexia, greater on the right, and a right extensor plantar response. In the following days the patient was intermittently lethargic. He developed a left extensor

## TABLE 1 CLINICAL COURSE

| *Case* | *Age (yrs), sex* | *Onset* | *Outcome* | *CT* | *Angiography and carotid Doppler sonography* | *Possible mechanism* |
|---|---|---|---|---|---|---|
| 1 | 61F | Stepwise onset with sudden deterioration and transient BP elevation | Gastrostomy, nursing home, severely impaired | PVL, bilat middle ⅓ posterior limb capsule extending superiorly | Unknown | Small vessel disease related to hypertension or diabetes |
| 2 | 68M | Stepwise onset with smooth deterioration | Gastrostomy, death within 1 yr of onset | R posterior ⅔ posterior limb internal capsule, L entire posterior limb | Doppler normal common carotid, suboptimal study for distal vessels, calcified carotids on x-ray | Small vessel disease related to hypertension |
| 3 | 67F | Stepwise onset, then sudden deterioration with abrupt BP drop | Gastrostomy, death within 1 mo of onset | Bilat middle ⅓ posterior limb internal capsule and adjacent globus pallidus extending superiorly | Doppler technically limited Angiographic narrowing of petrous carotid and attenuation of AchA on left | Small vessel disease related to hypertension or diabetes, intracranial atherosclerosis |
| 4 | 53F | Stuttering onset with waxing and waning symptoms then smooth deterioration | Home with moderate–severe impairment | PVL, R middle ⅓ posterior limb, L middle ⅓ posterior limb extending superiorly | Normal Doppler | Small vessel disease related to hypertension, diabetes, vasculitis, embolism of possible cardiac origin, possible atherosclerosis |
| 5 | 71F | Stepwise onset with abrupt deterioration | Gastrostomy, death within 1 mo , of onset | Bilat middle ⅓ posterior limb internal capsule extending superiorly | Unknown | Small vessel disease related to hypertension, radiation-induced vascular changes |
| 6 | 62M | Sudden onset and stepwise deterioration with transient BP elevation | Gastrostomy, rehab unit, near locked-in at 1 mo | R post limb internal capsule, and lateral geniculate, L posterior ⅔ posterior limb extending superiorly | Minimal atheroma bilaterally by Doppler | Small vessel disease related to hypertension or diabetes |
| 7 | 46F | Sudden onset with no deterioration | Home with moderate impairment | PVL R posterior ⅓ posterior limb internal capsule and adjacent globus pallidus, L mirror lesion | Normal Doppler | Small vessel disease related to hypertension |
| 8 | 79M | Stepwise onset | Death within 4 mo of onset | Bilat posterior ⅔ posterior limb internal capsule and adjacent globus pallidus extending superiorly | Unknown | Small vessel disease related to hypertension, diabetes; syphilis |

PVL = periventricular lucencies; AchA = anterior choroidal artery

TABLE 2. FURTHER CLINICAL DATA

| *Case* | *Cardiac disease* | *Previous stroke* | *Hypertension* | *Diabetes* | *Admission BP* | *Fasting blood glucose (mmol/l)* | *Smoking* | *Other* |
|---|---|---|---|---|---|---|---|---|
| 1 | Ischaemic heart disease | — | 10 yrs | — | 190/100 | 3.9 | 45 yrs, heavy | |
| 2 | Hypertensive | + | 7 yrs | — | 160/100 | 5.0 | | HbAS |
| 3 | Ischaemic heart disease | + | 20 yrs | 20 yrs | 220/120 | 26.9 | | |
| 4 | Ischaemic cardiomyopathy | + | 7 yrs | 1 yr | 220/106 | 10.8 | Heavy | HbAC + rheumatoid factor |
| 5 | Chronic AF, ischaemic heart disease | — | + | — | 160/110 | 5.1 | Heavy | |
| 6 | Not known | + | + | + | 200/100 | 12.8 | | |
| 7 | 1° AV block | + | Many yrs | — | 160/98 | 6.4 | | Elevated triglycerides |
| 8 | Ischaemic cardiomyopathy | + | 20 yrs | 20 yrs | 180/90 | 22.6 | | + RPR and FTA-abs. |

RPR = serum syphilitic reagin.

TABLE 3 MAXIMAL SYMPTOMS AND SIGNS

| | *Case* | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *1* | *2* | *3* | *4* | *5* | *6* | *7* | *8* |
| Lethargy | + | + | + | — | + | + | — | — |
| Pseudobulbar affect | — | — | + | + | — | — | + | + |
| Depression | — | + | — | + | + | + | — | — |
| Head or eye gaze preference | L | — | R | — | L | L | — | R |
| Visual field defect | — | ? | ? | — | ? | L homonymous hemianopia | ? | ? |
| Severe paralysis tongue, oropharynx | + | + | + | + | + | + | + | + |
| Mute | + | + | — | + | + | + | — | — |
| Hemiplegia | R then L | R arm | R arm | L leg | L | R | R, L leg | R face, L body |
| Hemisensory loss | R | ? | R | Bilat. | L | R | ? | ? |
| Quadriparesis | + | + | + | + | — | — | — | + |
| Urinary/bowel incontinence or retention | + | + | — | + | — | — | — | + |
| Extensor plantar responses | Bilat. | Bilat. | Bilat. | Bilat. | Bilat. | Bilat. | Bilat. | Bilat. |
| Other | R auditory neglect | | R tactile extinction | Cheyne-Stokes | Denial of deficit, L hemi-inattention, constructional apraxia | | | Confusion |

+ = present, — = absent, ? = unknown.

plantar response and left facial weakness, and was only able to grunt in a strained voice. He was now unable to protrude his tongue or to pucker his lips. The gag reflex was absent and the palate did not move on phonation. He was unable to swallow and frequently coughed and choked on his saliva. A gastrostomy was performed.

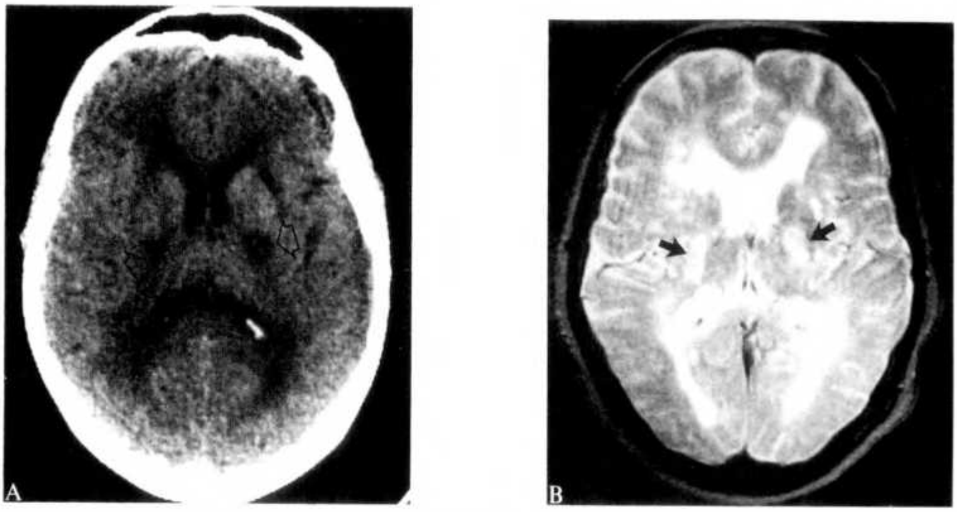

FIG. 1. Sequential bilateral development of infarction in the posterior limb of the internal capsule extending superiorly as shown in CT scan (A) and MRI (B) in *Case 1*.

A CT scan showed a new lucency in the middle third of the posterior limb of the right internal capsule and the entire posterior limb on the left. An MRI scan showed similar findings with the right-sided lucency in the posterior two-thirds of the posterior limb of the capsule (fig. 2). Tables 1–3 summarize the laboratory results.

One month after admission the patient remained bedridden and could communicate only with his left hand by pointing to a picture board with variable success. He was discharged to a rehabilitation centre 1½ months after admission. At 1 yr follow-up he was reported to be dead after aspiration pneumonia.

### *Case 3*

This obese 67-yr-old, right-handed woman had a 20 yr history of hypertension and diabetes mellitus. Three years before admission she had undergone an extracranial-intracranial bypass operation for a right hemisphere stroke believed to be related to stenosis of the petrous portion of the right internal carotid artery as defined by angiography. Her stroke had left her with a mild left hemiparesis. She now had an abrupt onset of slurred speech one evening. The following morning she awoke with increased dysarthria. Later that day, she became weak on the right and was unable to get off the toilet. On admission her blood pressure was 220/120 mmHg. This was reduced rapidly to 140/85 mmHg. Concomitantly her neurological state deteriorated; she was now lethargic and hemiplegic. The following day, still intermittently lethargic, she was able to cooperate on examination. Fits of uncontrollable laughter and a right motor neglect were present. Right tactile but no auditory or visual extinction was noted. The pupils were normal. She was unable to gaze fully conjugately to the right. The oculocephalic reflex was normal. A severe facial diplegia, mouth more than eyes, was present, worse on the right. She was markedly dysarthric and unable to swallow. She coughed on her saliva. Lip approximation was weak, and the range of movement, strength of protrusion of the tongue were severely limited. Lingual movements were slowed. Her soft palate drooped bilaterally and did not elevate on phonation. The gag reflex was absent on the right. Articulation was severely impaired and speech was limited to one syllable utterances. The voice was strained and hypernasal in quality. The right arm was paralysed, the leg weak and sensation on the right was depressed for pin-prick and touch, position sense being spared. The tendon reflexes were brisk and both plantar responses were extensor.

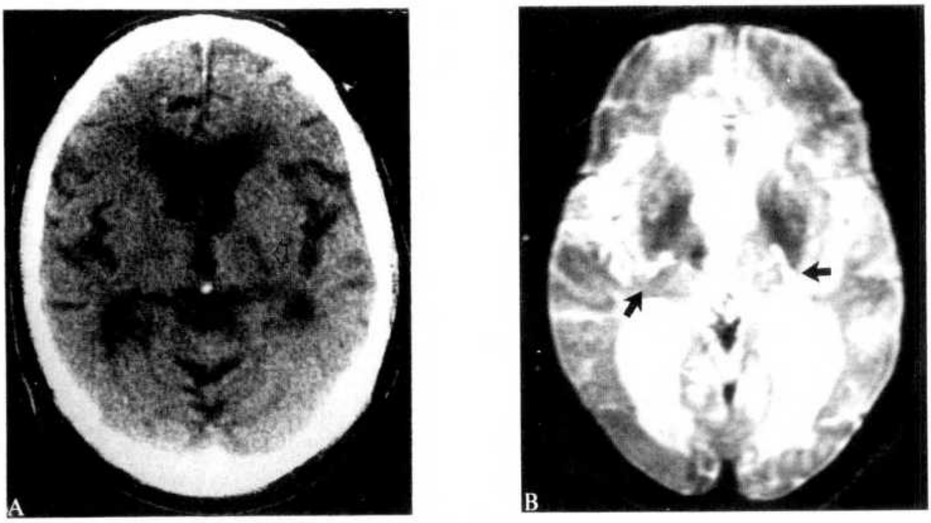

FIG. 2. CT scan (A) and MRI (B) in *Case 2* showing infarction in the posterior limbs of the internal capsules.

A CT scan showed bilateral lucencies in the posterior limb of the internal capsule in its middle third and the adjacent globus pallidus on the left with extension superiorly into the caudate nucleus and adjacent white matter immediately lateral to the lateral ventricle. Retrospective review of a CT scan performed in 1982 showed that the right capsular lesion was then present. It was now better defined in longitudinal extent. Tables 1–3 give other laboratory results.

A gastrostomy was performed and the patient's subsequent hospital course was marked by the new development of inferior myocardial ischaemia on ECG and ultimately by sudden respiratory followed by cardiac arrest and death 1 month after the onset of her symptoms.

### *Case 4*

This 53-yr-old right-handed woman had a 7 yr history of hypertension and a 1 yr history of diabetes mellitus and congestive heart failure. One year before she had had a stroke causing left-sided weakness from which she had largely recovered. For 2 weeks, she had had variable slurring of speech accompanied by a hoarse voice. Subsequently her speech progressed to unintelligible mumbling. She had also noted increased weakness of the left leg and a tendency to fall to the right. She was noncompliant with medications, a heavy smoker and had had intermittent urinary incontinence since the first stroke.

Blood pressure on admission was 220/106 mmHg, the pulse regular at 88/min. Cheyne-Stokes respiration was present. A systolic ejection murmur was present at the left sternal border. The patient was markedly dysarthric, had mild weakness of the left leg, bilateral hyperreflexia and extensor plantar responses. Over the following few days she showed increased dysarthria, dysphonia and hypernasality. She was unable to protrude her tongue. Lip and tongue movements were slowed and palatal elevation was absent on the right. She was dysphagic. A moderate facial diplegia was present, worse on the left. There was severe weakness of the left leg, increased weakness of the left arm, and bilateral hypalgesia of the face and left leg for pin-prick. Two weeks later, there was moderate improvement in her speech and swallowing and she was discharged to a rehabilitation centre with moderate dysarthria, resolved dysphagia, a right hemiparesis, and weakness of the left leg. One year later she was walking with the aid of a frame and, although otherwise unchanged, had uncontrollable fits of crying.

A CT scan showed a focal lucency in the middle third of the posterior limb of the internal capsule near its junction with the posterior third on the right. On the left, a focal lucency was seen in the middle third of the posterior limb of the capsule extending superiorly into the caudate nucleus and white matter adjacent and lateral to the lateral ventricle. A separate lucency was seen in the anterior limb of the capsule but the genu was spared. Periventricular lucencies were present. Other laboratory findings are summarized in Tables 1-3

### *Case 5*

This 71-yr-old woman had had bilateral radical neck dissection and radiation for oral cancer 8 yrs before. She was a heavy smoker and had a history of hypertension as well as of chronic atrial fibrillation. She suddenly developed slurred speech and mild weakness of the left face, arm and leg. On admission, her heart rate was irregular at 100 beats/min; blood pressure was 160/110 mmHg. She was intermittently lethargic and had a blunted affect. She denied any new deficit until specifically asked. She bisected a line to the right of the midpoint and had mild difficulty copying a design. There was a right gaze preference and incomplete conjugate gaze to the left. Her right pupil was smaller than the left, but this was of long standing There was marked left facial weakness, mouth more than eye, as well as reduced forehead wrinkling on that side. Her mouth hung open at rest and she was unable to close it. Her dysarthria was severe and her voice low-pitched and hypernasal. The gag reflex was depressed, more so on the left, and palatal elevation on phonation was absent. Tongue movements were slow and restricted in range. A mild left hemiparesis was present, face and arm more than leg, worse proximally. There was tactile extinction for touch on the left as well as reduced appreciation of temperature and pin-prick which had a dysaesthetic quality. Position sense was intact. The tendon reflexes were brisk bilaterally and both plantar responses were extensor. Two days later the patient deteriorated abruptly. Although more alert, there was no initiation of speech and she had a marked facial diplegia, involving eye closure, forehead wrinkling and mouth movement. Dysphagia was severe. Her blood pressure was 210/128 mmHg.

A CT scan showed bilateral internal capsule lucencies, located in the middle third of the posterior limb and extending superiorly into the caudate nucleus and adjacent white matter immediately lateral to the lateral ventricle. Tables 1-3 give other laboratory findings.

A gastrostomy was performed. There was no clinical improvement and 4 weeks after admission, the patient died in a nursing home of sudden cardiorespiratory arrest.

### *Case 6*

This 62-yr-old right-handed man 4 yrs before admission had undergone craniotomy for removal of a pituitary adenoma. Since then, he had received thyroid and steroid replacement medication and had developed diabetes. One year before admission he had had an episode of transient dysarthria. On the day of admission, while kneeling and praying aloud, his speech suddenly became slurred and he had momentary bilateral arm and leg weakness accompanied by tingling. On admission, blood pressure was 200/100 mmHg and the pulse was 96/min. An old left homonymous hemianopia was noted. The pupils reacted sluggishly to light; this had also been noted previously. There was left head and eye gaze preference. His eyes moved slowly and inconsistently but conjugately to the right. The oculocephalic reflex was intact. A depressed right corneal reflex was noted. He had facial diplegia, the right eye and mouth muscles being severely affected, the left moderately so. Forehead wrinkling was diminished on the right. He could pucker his lips but at rest they gaped open. Jaw strength was normal but palatal elevation on phonation was weak. He had severely limited protrusion of the tongue and tongue movements were weak and slow. The gag reflex was absent, and the patient coughed and choked on his saliva. Involuntary smiling was preserved. His voice was strained and hypernasal. A moderate right hemiparesis was present, the arm and leg being affected equally. Diminished pin-prick appreciation on the right, bilateral hyperreflexia, left more than right and a right extensor plantar response were also found. Over the next 24 h the patient had a transient blood pressure rise of 240/120 mmHg and his condition deteriorated. He became totally hemiplegic and mute, able only occasionally to grunt. Lip movement was severely restricted and he was unable to move the tongue. He was lethargic and had Cheyne-Stokes respiration. Nonetheless he remained responsive and cooperative to command. Sensory deficit to deep pain and pin-prick was now severe on the right. A CT scan on the day after admission showed a lacunar infarct in the posterior third of the posterior limb of the right internal capsule. MRI 4 days after onset showed a new lesion in the posterior limb of the left internal capsule in its posterior two-thirds and the adjacent globus pallidus, with superior extension into the adjacent caudate nucleus and white matter immediately lateral to it. Repeat CT showed evolution of the right-sided lesion which was now better defined.

A gastrostomy was performed. Minimal improvement of facial and tongue movement occurred and he was moved 3 weeks after the onset of his stroke to a rehabilitation unit. Hemiplegic and mute, he was able to communicate only by weakly nodding his head and using his left hand to point.

*Case 7*

This 46-yr-old woman had a history of four previous strokes, with a residual moderate right hemiparesis and mild dysarthria. She is hypertensive and has had seizures for many years but has been noncompliant with medication. She suddenly developed increased slurring of speech, inability to swallow, increased right-sided and new left-sided weakness, and inability to walk. Blood pressure on admission was 160/98 mmHg, the pulse regular, 76/min. Her left radial pulse was weaker than the right. Uncontrollable fits of laughter occurred, but she denied any emotional content for these outbursts. Her left pupil was unreactive to light. Her jaw jerk was increased and there was left facial weakness of moderate severity affecting eye closure and mouth movement. The palate drooped at rest and did not elevate fully on phonation. The gag reflex was absent on the left. Lip and tongue movements were slow, weak and awkward and her voice was strained, harsh and hypernasal. Her speech was explosive and severely distorted. The right arm and leg were mildly but equally weak and there was a left foot drop. Both plantar responses were extensor.

A CT scan showed a discrete lucency in the upper portion of the posterior third of the posterior limb of the right internal capsule near the junction with the middle third and adjacent medial globus pallidus. On the left there was a well defined lucency in the mirror position in the posterior limb of the internal capsule. Periventricular lucencies were noted.

The patient was discharged to a rehabilitation centre where she improved her gait and swallowing ability. She did not require a gastrostomy. Six months later she was unchanged.

*Case 8*

This 79-yr-old man had a 20 yr history of hypertension, diabetes mellitus and more recent chronic renal insufficiency as well as peripheral vascular disease necessitating a right leg amputation. He was noncompliant with medications. Eight years before he had had a stroke which left him with a moderate right spastic hemiparesis. One day before admission he suddenly became unable to move his left arm or leg and seemed confused. Two months previously, he had had intermittent bladder and stool incontinence and 3 days before admission had complained of chest pain, became unable to speak clearly or swallow, and regurgitated his food. Blood pressure on admission was 189/90 mmHg; the pulse was regular, 82/min. He was obese and had fits of uncontrollable crying for which he denied any emotional content. There was motor impersistence for eye closure and no recognition of the new left hemiparesis. His pupils reacted sluggishly to light. There was a right gaze preference, but conjugate eye movements were full. A severe right facial weakness affecting voluntary forehead wrinkling, eye closure and smiling was present. On the left, moderate similar deficits were present. He had decreased palatal elevation on phonation and his voice was hoarse and hypernasal. Food pocketed in both cheeks and swallowing was delayed. There was a right spastic hemiplegia, tone was increased in the left arm and leg. The left arm was moderately paretic the leg mildly so. On sensory testing, his replies were inconsistent for pin-prick and touch, but position sense was intact. The tendon reflexes were brisk, especially on the right, and the left plantar response was extensor.

CT scanning revealed bilateral lucencies in the posterior two-thirds of the posterior limbs of the internal capsules, each extending into the adjacent medial globus pallidus and superiorly into the caudate nucleus and white matter immediately lateral to it, especially on the left. His blood FTA test was positive.

While in the hospital, the patient developed chest pain of acute onset lasting for 20 min, but without new ECG findings. Over the week following admission, his pseudobulbar symptoms improved slightly as did his left-sided weakness and he was able to return home. Three months later he had a fatal cardiorespiratory arrest at home.

## DISCUSSION

Mutism of sudden onset with pseudobulbar palsy has rarely been attributed to circumscribed bilateral capsular infarction. In our 8 cases, sequential bilateral capsular destruction with interruption of efferent pathways from the motor speech cortex to the bulbar apparatus produces mutism with paralysis of face, oropharynx and tongue.

Marie (1906) described acute anarthria without aphasia due to unilateral lentiform nucleus haemorrhage. He postulated an 'anarthric' area of brain, the destruction of which would cause the loss of speech. This area lies between transverse lines drawn from the anterior and posterior limits of the insula to the lateral ventricle and medial border of the hemisphere and includes these structures. More particularly he considered that the 'zone lenticulaire', white matter between the insula and lentiform nucleus and including the external portion of the latter, to be the area responsible for anarthria in his case. His patient had a caudato-putaminal-capsular haemorrhage at autopsy. The presence of associated pseudobulbar symptoms in his patient was not mentioned. Our patients with bilateral capsular-pallidal infarcts have in addition to anarthria, bulbar, hemimotor and hemisensory signs. As seen by CT scan and MRI their strokes lie posteriorly and medially in Marie's 'lesion d'anarthrie', in the territory of the anterior choroidal artery (AchA).

Unilateral infarction of the AchA territory has been discussed recently by Decroix *et al.* (1986), Helgason *et al.* (1986) and Bogousslavsky *et al.* (1986). None of these patients showed pseudobulbar features and only one was mute. However, dysarthria was a common finding and found in 2 out of 5 cases of Helgason *et al.*, 6 out of 16 of Decroix *et al.* and all those of Graff-Radford *et al.* (1985). We have seen one unreported case of unilateral AchA territory infarction accompanied by severe bulbar dysfunction, right hemiplegia and hemisensory loss. He had severe dysarthria, right-sided facial paralysis, tongue deviation to the right, absent palatal movement and total inability to swallow. Unlike the bilateral cases, he made a rapid recovery. The patient needed a gastrostomy tube but over 8 weeks regained total ability to speak and swallow. A CT scan revealed a lucency in the posterior limb of the left internal capsule extending into the adjoining caudate nucleus adjacent to the lateral ventricle in the territory of the AchA.

Case 16 of Decroix *et al.* (1986) with unilateral AchA territory infarction presented with an initial loss of speech (mutism), a moderate right hemiparesis with faciobrachial predominance, and ataxia of the right arm. A new lucency in the capsular posterior limb on the left was found, but an old contralateral anterior limb lucency was present. The clinical significance of the latter is unknown. There was no mention of other bulbar dysfunction. This case represents the only reported case of unilateral AchA infarction with mutism.

Unilateral pseudobulbar paralysis has been described in unilateral capsular infarcts. Reports have emphasized the genu as the site of pathology. Iwata (1984) reviewed a case of unilateral palatal paralysis which he believed was caused by unilateral interruption of the corticofugal motor pathway at the level of the corona radiata and adjacent capsular genu. A small left lenticulocapsular haematoma which presented as right faciobrachial paresis, dysarthria and right lingual paresis was described by Bogousslavsky and Regli (1984) as an incomplete 'opercular' syndrome. Again the capsular extent of the lesion was limited to the genu and anterior part of the posterior limb. Langworthy and Hesser (1940) reviewed unilateral injury of corticobulbar fibres. This may cause transient loss of function of bulbar muscles supplied by cranial nerves V and VII as well as gaze preference. Minimal palatal elevation with deviation of the uvula to the unaffected side, pharyngeal and laryngeal symptoms can occur and the tongue may be more severely as well as permanently affected as in our unreported patient with unilateral AchA territory infarction.

It would seem justifiable to conclude that unilateral capsular infarcts can on rare occasions present with acute mutism and pseudobulbar signs. Mutism when due to infarction at capsular level depends on the presence of bilateral disease, and may often be traced to infarction in the territory of vascular supply of the AchA, in a capsular-pallidal distribution.

Few accounts of mutism due to bilateral internal capsular infarction exist. Fisher (1979) examined a man (his Case 5) who had infarcts which were of lacunar size, of different ages, the older being localized pathologically to the midportion of the posterior limb of the internal capsule on the right, the more recent to the capsular genu on the left. This patient had had a previous left hemiparesis which had begun acutely 3 months before and from which he had almost entirely recovered. The more recent stroke began suddenly with right-sided weakness, aphonia and total paralysis of the lips and tongue. The patient had had hypertension of long standing. At necropsy stenosis of the lumen of branches of the AchA was found bilaterally. In places arterial wall pathology appeared to be atheromatous in nature, at others lipohyalinotic. Leys *et al.* (1985) reported a case of sudden paralysis of facio-labio-glosso-velo-pharyngeal distribution without limb weakness due to bilaterally symmetric genu-corona radiata junction infarction. The lesion was identified by CT scanning and attributed to watershed ischaemia of the territory supplied by the external lenticulostriate branches of the middle cerebral artery and end branches of the posterolateral choroidal artery. Leys *et al.* postulated undocumented hypotension to be responsible. A single case of acute pseudobulbar palsy ascribed to bilateral capsular infarction lying in AchA territory of vascularization was reported by Buge *et al.* (1979). The patient suddenly developed paralysis of lingual, pharyngeal and laryngeal function accompanied by severe dysarthria, facial diplegia, worse on the right, limited vertical movement of the right eye, and bilaterally brisk tendon reflexes. At necropsy, bilateral symmetric posterior limb capsular-medial globus pallidus infarcts were delineated. The old infarct on the right had no clinical correlate from the history. The aetiology was judged to be thromboembolic, with emboli arising from ipsilateral proximal internal carotid artery atheroma. The patient was a heavy smoker, had an atrial septal defect, and was hypertensive and diabetic. Thus embolism of cardiac origin or intrinsic small vessel disease possibly played a pathogenic role. Chia (1984) had a patient with tetraplegia, mutism and total paralysis of the face, jaw, tongue and palate, and for gag and coughing. The patient was young and had no history of diabetes, hypertension or heart disease. The precipitating event was haemorrhagic shock. CT scanning showed lucencies localized to the posterior limbs of both internal capsules and the caudal parts of the genu in the end zone of supply of branches of the posterior communicating arteries. The patient of Mohr (1986) had an abrupt onset of anarthria, severe dysphonia and dysphagia with mild right arm weakness. Infarcts of sequential appearance as defined by CT scanning were responsible. The addition of a new lacune in the genu of the left internal capsule to a previously identified infarct in the posterior limb on the right yielded the acute symptoms.

The infarctions in our cases were localized to the posterior limb of the internal capsule and medial globus pallidus (*see* fig. 3). They resemble the case of Buge *et al.* (1979) anatomically as well as clinically. In 6 patients the lesions extend superiorly to involve an area immediately lateral and adjacent to the lateral ventricle. This site most probably represents the caudate nucleus and white matter immediately lateral to it, the most inferior portion of the corona radiata. The lucencies noted in our patients on the higher CT cuts represent the extension of an AchA infarct, particularly when seen to occur in direct continuity with those noted in the CT cuts below (H. Damasio, personal communication). Damasio has justly indicated that the AchA supplies the tail of the caudate nucleus. When infarcted in its superior and anterior portion, a lucency would appear on CT scanning immediately adjacent to the lateral ventricle. Damasio's CT template (Damasio, 1983, 1987) and the definition of cerebral arterial supply obtained by the injection of 87 brains (Beevor, 1907) show AchA territory images very similar to the location of stroke in our patients.

In all our cases except one (Case 2), the posterior two-thirds of the internal capsule was involved. Importantly, the genu of the internal capsule was never involved. Other authors have emphasized corticobulbar interruption at the genu as causative for pseudobulbar symptoms and mutism. The genu was infarcted in the patients of Fisher (1979), Leys *et al.* (1985), Chia (1984) and Mohr (1986). This was not so in the case of Buge *et al.* (1979) who, as our patients, had lesions of the middle third of the posterior limb of the internal capsule and medial globus pallidus. Our infarcts are documented by CT scanning and correspond to the CT localization of the AchA territory of vascular supply made by Damasio (1983), Takahashi *et al.* (1980) and Sterbini *et al.* (1987) (*see* fig. 3).

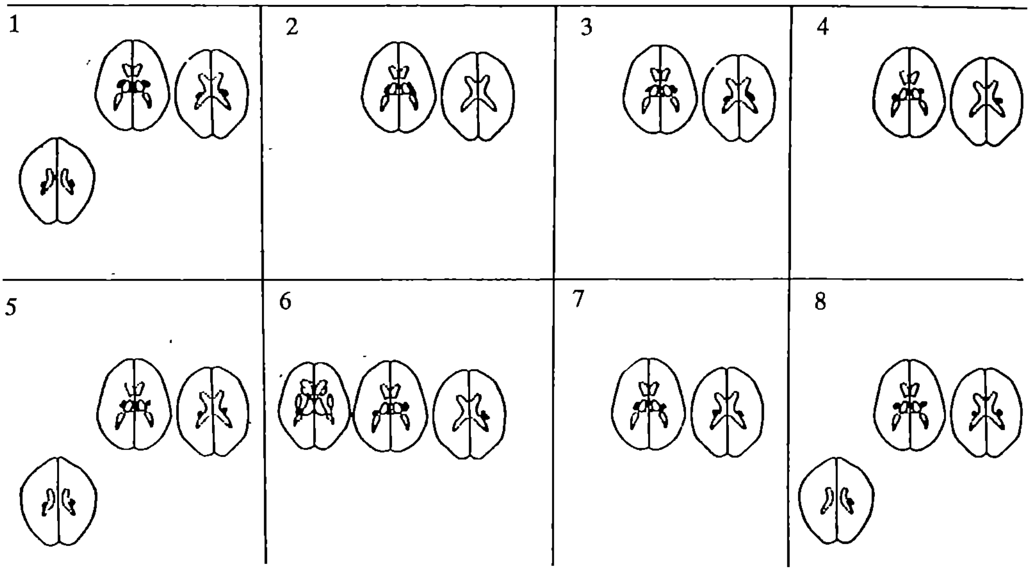

FIG. 3. Diagrammatic representation of location of infarcts in *Cases 1–8*.

Although it is likely that interruption of the corticobulbar tracts caused pseudobulbar mutism in our patients, it is possible that other structures crossing the posterior limb of the internal capsule were affected (Marie and Guillain, 1902). Pallidofugal fibres originating in the medial globus pallidus and travelling through and near the posterior limb to end in the ventrolateral and ventroanterior thalamus include the ansa and fasciculus lenticularis. Bilateral thalamotomy has been complicated by dysphonia, dysarthria and dysphagia following selective lesions of the Vim, Vce, Vci and Cem nuclei (Andrew *et al.*, 1983). Word blocking has occurred after selective bilateral destruction of the ventrolateral thalamic nuclei (Matsumoto *et al.*, 1984).

Although no definite necropsy or arteriographic proof of AchA occlusion exists, we believe that clinically our cases represent the first reported series of the syndrome of bilateral anterior choroidal artery territory infarction. They present features of the few previously reported single cases of bilateral AchA infarction as well as a combination of elements of the unilateral AchA syndrome. Abbie (1933), Buge *et al.* (1979) and Fisher (1979) described the only reported cases of bilateral infarction in the AchA territory. These cases, when considered with ours, delineate a spectrum of clinical signs of bilateral AchA territory infarction. Abbie's case had no pseudobulbar symptoms or mutism as were present in the cases of Buge *et al.* and Fisher, but had instead bilateral superior quadrantanopia of acute onset. Abbie's patient had the complete triad of AchA territory infarction, namely a homonymous visual field defect, in this case a superior quadrantanopia, hemiparesis and hemisensory loss on the right, together with a superior quadrantanopia on the left. Our cases resemble those of Buge *et al.* and Fisher in the presence of pseudobulbar mutism, but lack the visual field abnormalities of Abbie's patient. Case 6 had a left homonymous hemianopia which could have been due to infarction of the geniculocalcarine tract at its origin in the AchA territory on the right. It was considered, however, that it had occurred after removal of his pituitary adenoma several years before. Visual field testing was attempted only in 2 other of our patients (Cases 1, 2), but without success because of their inability to communicate. Deficits of this nature may, therefore, have been overlooked. All our cases, as did those of Abbie, Buge *et al.* and Fisher, had hemiparetic and hemisensory symptoms explained by interruption of the corticospinal and sensory radiations in the posterior limb of the internal capsule. Abbie's patient, who was a young woman with syphilis, 2 months before the sudden onset of bilateral homonymous superior quadrantanopia, had developed a hemiparesis, and a hemisensory deficit for all modalities with hyperreflexia and an extensor of plantar response on the right. Fisher's case did not have hemisensory signs or visual field defects, nor did the case reported by Buge *et al.* Abbie's case at necropsy showed necrosis of both lateral geniculate bodies with degeneration of the cerebral peduncles. The postmortem description of the brain at the time of Abbie's report was incomplete and information on capsular or globus pallidus pathology is lacking.

Mirror AchA infarctions are acquired sequentially. The time interval between the appearance of bilateral lesions in reported cases has been short, being 2–3 months in Fisher's and Abbie's patients, although it was undefined in the case of Buge *et al.* The bilaterality in our patients was acquired in time ranges of hours (Case 6), days to weeks (Case 1), months to under 10 yrs (Cases 2, 3, 4, 7, 8) and undefined in Case 5. The rapid acquisition of bilateral capsular lesions may reflect an advanced stage of arterial wall pathology in the AchAs, or the presence of a source for repeated cardiac emboli or untreated syphilis (Case 8).

The time from onset of symptoms to maximal neurological deficit varied. One of our cases had a true capsular warning syndrome (Case 1). This has been noted before in a case of AchA territory infarction (Donnan and Bladin, 1987). In 3 cases, there was a waxing and waning of symptoms for several days before medical attention was sought (Cases 4, 7, 8). Other patients were mute within minutes to hours of the onset (Cases 1, 2, 6), while some became increasingly pseudobulbar in a stepwise manner and then mute within days of the onset of bulbar dysfunction

(Cases 3, 5). The patients of Abbie, Fisher and Buge *et al.* had deficits which were sudden and maximal within minutes of onset.

The outcome in all of our cases was poor. Three out of the 8 patients were dead within 3 months (Cases 3, 5, 8) and 1 (Case 2) within a year of the onset of pseudobulbar mutism. Of those who remain alive, all are severely impaired. Death was precipitated in at least 1 case by a respiratory arrest (Case 3) and aspiration pneumonia in another (Case 2). Details of the other 2 deaths are not available. Two patients (Cases 2, 8) had evidence of myocardial ischaemia and all had the potential to aspirate.

The pathogenesis of ischaemic stroke in our cases is similar to that offered by Abbie, Fisher and Buge *et al.* Hypertensive small vessel disease must have been present in our patients as all had a history of elevated blood pressure. In most cases this was untreated. The patients of Fisher and Buge *et al.* were hypertensive, and the case reported by Buge *et al.* had diabetes, as did half of our cases. Abbie's patient had syphilis and at postmortem a syphilitic endarteritis of both anterior choroidal arteries was found. One of our cases (Case 8) had syphilis but refused lumbar puncture, thus making a diagnosis of meningovascular syphilis unverifiable. The case of Buge *et al.* had a patent foramen ovale. Five of our patients had evidence of cardiac disease. Case 5 had chronic atrial fibrillation and the others ischaemic myocardial disease. Fisher found atheroma of the AchA in his patient at postmortem. Of our cases at least one patient (Case 3) had angiographically documented intracranial atheroma of the internal carotid artery proximal to the AchA. The patient of Buge *et al.* and our Cases 2 and 6, had bilateral extracranial internal carotid artery atheroma. Where deaths occurred in our series, autopsy was denied, so that detailed pathological confirmation of vascular disease was not possible.

All our patients had elevated blood pressure on admission (Table 2). A sudden rapid rise in blood pressure was associated with the onset and worsening of stroke in at least 3 of our patients. Recent evidence (Dutka *et al.*, 1987) supports the concept of limitation of reperfusion after ischaemia because of the potentiation of endothelial damage through the interaction between cellular elements in the blood and the coagulation and complement systems during transient elevation of blood pressure in the immediate poststroke period. One patient, however, worsened as her blood pressure fell precipitously on a background of chronic hypertension and probable altered cerebral autoregulation.

Certain clinical features shown by our patients bear mention. The majority had a period of lethargy with or without Cheyne-Stokes respiration. Bilateral occlusion of the AchA in surgery for parkinsonism has been followed by lethargy (Cooper, 1956). Four patients had uncontrollable fits of laughter or crying devoid of emotional content. Others had marked depression or blunted affect. Hypothalamic and pallidal efferent fibres mediating emotional impulses to the bulbar cranial nerve nuclei do not travel in the internal capsule and are spared in our patients (Brodal, 1981). The role played by caudate destruction with regard to changes in affect has yet to be defined. Abnormality of ocular movement with head and eye gaze preference has been reported in unilateral AchA stroke (Helgason *et al.*, 1986) and in several of our present cases. It is reminiscent of deep putaminal infarcts or haemorrhages and large hemisphere strokes. Head and eye gaze preference in our patients appeared to be related to neglect. This and other dysfunctions of visuospatial ability or language are well recognized in unilateral AchA syndromes (Cambier *et al.*, 1983; Decroix *et al.*, 1986; Helgason *et al.*, 1986). Urinary and bladder incontinence was noted in almost all our cases, but no patient was severely demented. Alajouanine and Thurel (1933*b*) have discussed the independence of emotional and urinary incontinence due to bilateral upper motor neuron interruption from dementia.

## *Conclusions*

In this paper, we have presented 8 instances of pseudobulbar mutism of abrupt onset due to discrete lacunar or slightly larger infarcts localized by CT and MRI to the posterior limb of the internal capsule, the medial globus pallidus and the adjacent caudate nucleus and white matter in the area of supply of the AchA. We do not have proof that the AchA was occluded. Our basis for implicating its involvement rests on our CT-MRI definition of vascular supply (Beevor, 1907; Damasio, 1983, 1987, personal communication). Although there was no necropsy confirmation of the pathogenesis of the strokes in our patients, the possibility exists that emboli of cardiac as well as atheromatous arterial origin, and small vessel disease related to hypertension, diabetes or intracranial atheroma, were present in our cases. Poorly controlled hypertension and acute transient elevation of blood pressure were common to all our cases. Both therefore appear to play an intimate role in the pathogenesis of stroke in our patients.

Bilateral AchA territory infarction reflects an advanced stage of cerebrovascular disease and carries a poor prognosis. It can be recognized by clinical signs and confirmed by CT scanning and MRI. Although acute pseudobulbar symptoms with various degrees of mutism have been described in unilateral and bilateral cortico-opercular (Tournier, 1898; Foix *et al.*, 1926; Alajouanine and Thurel, 1933*a*; Alajouanine *et al.*, 1959; Boudin *et al.*, 1960), lenticular (Marie, 1906) or brainstem (Karp and Hurtig, 1974) location, it is the presence of additional elements of the unilateral AchA syndrome and the lack of definite brainstem signs, in combination with a previous history of stroke localizing to the internal capsule, which characterize the nature of the lesion. Assiduous investigation and recognition of underlying vascular or cardiac disease and treatment at the stage of unilateral capsular infarction may prevent the occurrence of contralateral capsular ischaemia. Careful control of blood pressure in the acute stages of ischaemia may prevent postischaemic deterioration which often leaves the patient virtually in a locked-in and moribund state.

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# TEMPORAL ORDERING AND SHORT-TERM MEMORY DEFICITS IN PARKINSON'S DISEASE

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## SUMMARY

Previous studies of remote memory function have indicated a dissociability between memory for the content and date of past events and suggested selective deficits of dating capacity in Parkinson's disease (PD). The present study examined the hypothesis that poor dating in PD is linked to a specific deficit in temporal contextual memory which also affects new learning. Patients with PD and patients with Alzheimer's disease (AD) were compared in their ability to perform tasks of content recognition and recency discrimination of words presented sequentially. Compared with AD patients, PD patients were disproportionately impaired in recency discrimination relative to content recognition. When performance was analysed as a function of retention interval, AD patients showed impairment in both tasks at all intervals. PD patients, by contrast, showed deficits in content recognition at the short stimulus-test intervals only, possibly reflecting the clinical phenomenon of bradyphrenia. These results suggest that recency discrimination deficits and impaired short-term memory processing are specific cognitive deficits in PD that may be linked to subcortical deafferentation of the frontal lobes.

## INTRODUCTION

In a previous study (Sagar *et al.*, 1985*a*, 1988) we showed that patients with Parkinson's disease (PD) were impaired in their capacity to date past public events despite preserved ability to recognize those events; this deficit was greater than occurred in Alzheimer's disease (AD). We postulated that dating past events may require cognitive mechanisms distinct from those involved in the recognition of content of those events and that in PD the former process may be selectively disrupted.

The ability to date past historical events is a complex one including rote learning and reconstructive memory (Friedman and Wilkins, 1985). It is probable, however,

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that part of this reconstructive process involves judgements of recency between the event to be dated and highly salient personal events of high memorability for which the date is known as a fact (Loftus and Marburger, 1983). In normal subjects (Hasher and Zacks, 1979), amnesic patients (Huppert and Piercy, 1976; Hirst and Volpe, 1982; Sagar *et al.*, 1984; Mayes *et al.*, 1985; Meudell *et al.*, 1985) and epileptic patients treated with focal cortical excision (Milner, 1971, 1974; Corsi, 1972) the ability to make judgements of recency in new learning was dissociable from the capacity to recognize previous events, suggesting that recognition memory and recency discrimination are served by independent cognitive processes.

Thus, to the extent that the ability to date past public events involves judgements of recency, we predicted that patients with PD would show a deficit in recency discrimination when content recognition memory was intact. Accordingly, we examined recognition memory and recency discrimination in patients with PD. Results in PD were compared with those in AD so as to establish the nonspecific effects of dementia; performance was measured at several retention intervals so as to compare the course of forgetting of the different functions.

## METHODS

### *Subjects*

The subjects were 15 patients with PD, 15 patients with AD and 15 healthy control subjects (Table 1). The patients were drawn from the Memory Disorders Unit and the Movement Disorders Unit at the Massachusetts General Hospital. The diagnosis of AD was based on strict inclusion and exclusion criteria (McKhann *et al.*, 1984; Khachaturian, 1985). The diagnosis of PD was based upon the presence of 2 of the 3 clinical criteria of akinesia, rigidity and rest tremor, and a positive response to antiparkinsonian medication. None of the patients had a past history of stroke or any abnormal neurological signs other than those of PD The PD patients were not selected by any behavioural criteria. At the time of testing, all PD patients were treated with antiparkinsonian medication, in the majority of cases a levodopa preparation. All AD and PD patients were ambulant and free from psychiatric disease. Neither patient group was treated with any primarily psychoactive medication. The groups were matched for age and years of education but the PD group had a higher male: female sex ratio than the other two groups. The PD group had a longer mean duration of illness ($P < 0.01$),

TABLE 1. CHARACTERISTICS OF SUBJECT GROUPS. MEANS AND RANGE

| *Group* | *Age (yrs)* | *Education (yrs)* | *Duration of disease (yrs)* | *Blessed Dementia Scale score** |
|---|---|---|---|---|
| Control | 63.1 | 13.7 | Not | 0.3 |
| (7 M, 8 F) | (54–77) | (10–19) | applicable | (0–2) |
| Parkinsonian | 62.5 | 15.4 | 6.0 | 3.0 |
| (13 M, 2 F) | (39–80) | (8–20) | (1–13) | (0–12) |
| Alzheimer | 63.5 | 14.9 | 3.2 | 8.6 |
| (7 M, 8 F) | (53–76) | (12–20) | (2–7) | (5–16) |

* Memory and orientation section. M = male; F = female.

but was less demented as judged by performance on the memory and orientation section of the Blessed Dementia Scale (BDS) (Blessed *et al.*, 1968). Three of the 15 PD patients were clinically demented according to criteria of the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM III).

### *Procedure*

The Verbal Temporal Ordering (VTO) Test, modified from Hirst and Volpe (1982), consisted of a series of 493 nouns which were displayed on a computer screen at a rate of one every 2 s. Each word contained 4, 5 or 6 letters and had a frequency rating in the English language of 25 times per million or more (Kučera and Francis, 1967). At random intervals throughout the display, one of two types of item appeared on the screen: content recognition tests contained a previously presented word and a foil; recency discrimination tests contained 2 previously presented words. The test questions 'Which of these words have you seen on this test?' or 'Which of these words did you see more recently?' appeared at the top of the screen and were also spoken by the examiner. The two alternative answers subsequently appeared side-by-side underneath the question on the screen.

The test questions appeared at various intervals after stimulus presentation. The duration of each stimulus-test interval was defined as the number of intervals between events where an event was either another stimulus word or a test question. For example, where a question immediately followed stimulus presentation, the stimulus-test interval was 1 and there were no intervening events; where a question was the third item after stimulus presentation, the stimulus-test interval was 3 and there were 2 intervening items that could be stimulus words or test questions relating to earlier stimulus words. The position of a content recognition question was defined by one such interval. Recency discrimination questions examined 2 previously presented words; the position of a recency discrimination question was therefore defined by two intervals, one corresponding to each word examined in the test.

For content recognition, the stimulus-test intervals were 1, 3, 6, 10, 15, 25, 50, 100 and 150; there were five exemplars at each position. For recency discrimination, all possible pairings of these stimulus-test intervals were used (1–3, 1–6, 1–10 . . . 50–100, 50–150, 100–150); there were 5 exemplars for each pairing.

Test questions were presented in random order, subsequently modified to equalize the proportion of test questions and single-word stimuli within each stimulus-test interval. The 2 words presented as choice responses in each test of content recognition or recency discrimination were matched for word length and frequency. For each stimulus-test interval, the 5 exemplars of each type of test (content recognition or recency discrimination) were matched for word length and frequency to the list as a whole; content recognition and recency discrimination test responses were similarly matched to each other. In the two-choice tests, 50% of the correct responses appeared on the left half of the screen and 50% on the right half of the screen in random order.

During administration of the test, subjects were seated beside the examiner and in front of the screen. They were instructed to read each word aloud and to remember the words in their order of appearance. Subjects gave oral responses to the questions in unlimited time. The examiner entered the response into the computer at the same time as he instructed the subject 'Keep on reading'. The registration of the response triggered the appearance of the next stimulus word.

### *Statistical analysis*

Results were calculated separately for content recognition and recency discrimination as the mean percentage correct at each stimulus-test interval. For recency discrimination in some analyses, results were pooled for each position of the more *recent* stimulus and performance was assessed across stimulus-test intervals corresponding to the more recent stimuli of the pairs. Other analyses examined the effect on performance of increasing interstimulus intervals: for each position of the recent stimulus, the results were analysed according to the position of the more *remote* stimulus. Total percentage correct was the mean of the average performances at each stimulus-test interval.

Repeated measures analyses of variance (ANOVA) of Group (G) × Task (content or recency) (T) × Interval (I) were performed separately for the scores on the VTO test. Arc sin square root transformations were used to produce normal distributions of data with homogeneous variances. For statistical purposes, all stimulus-test intervals were examined separately. In graphic representations, however, results were pooled for intervals beyond the theoretical limit of short-term memory (i.e., intervals greater than 6) as 10, 15, 25 and 50, 100, 150 so as to eliminate irregularities in the forgetting curve that may have resulted from reduced numbers of data points at longer intervals. When ANOVA yielded significant differences among data sets, planned paired comparisons were performed using the Mann-Whitney U Test or the Wilcoxon Matched-Pairs Signed-Ranks Test (two-tailed unless otherwise stated).

## RESULTS

### *Total scores*

In all subject groups, recency discrimination was more difficult than content recognition (for VTO, $F(1, 42) = 182.89$, $P < 0.001$). Significant differences emerged among groups, however, in their performance on content recognition and recency discrimination (Table 2) (for total scores across groups on the VTO test $F(2, 42) = 11.08$, $P < 0.001$). The interaction G × T was significant ($F(2, 42) = 3.32$, $P < 0.05$), indicating a difference among groups in their relative performance in content recognition and recency discrimination.

TABLE 2 TOTAL SCORES AND PERFORMANCE AT EACH STIMULUS-TEST INTERVAL ON THE VERBAL TEMPORAL ORDERING TEST*

| Stimulus-test interval | *1* | *3* | *6* | *10* | *15* | *25* | *50* | *100* | *150* | *Total* |
|---|---|---|---|---|---|---|---|---|---|---|
| Content | | | | | | | | | | |
| Control | 100 | 96.0 | 85.3 | 74.7 | 88.0 | 77.3 | 77.3 | 72.0 | 64.0 | 81.6 |
| | (0) | (2.14) | (4.6) | (5.3) | (4.7) | (5.5) | (5.1) | (5.8) | (6.5) | (1.9) |
| PD | 84.0 | 85.3 | 85.3 | 76.0 | 81.3 | 72.0 | 66.7 | 73.7 | 58.7 | 75.8 |
| | (6.2) | (3.8) | (5.0) | (5.2) | (4.9) | (4.3) | (5.7) | (4.2) | (5.7) | (2.5) |
| AD | 89.3 | 73.3 | 76.0 | 66.7 | 56.7 | 69.3 | 68.0 | 65.3 | 53.3 | 68.4 |
| | (3.8) | (5.0) | (5.9) | (6.7) | (5.3) | (4.7) | (4.3) | (4.6) | (5.0) | (2.8) |
| Recency | | | | | | | | | | |
| Control | 96.2 | 82.2 | 71.7 | 66.1 | 59.7 | 62.6 | 58.7 | 54.7 | — | 69.0 |
| | (0.9) | (2.5) | (1.8) | (2.5) | (2.9) | (3.4) | (3.4) | (5.0) | — | (1.3) |
| PD | 84.9 | 72.2 | 61.4 | 63.5 | 57.7 | 56.1 | 56.0 | 50.0 | — | 62.7 |
| | (4.3) | (2.8) | (2.8) | (1.8) | (2.6) | (4.1) | (3.0) | (5.4) | — | (1.6) |
| AD | 87.7 | 64.7 | 59.3 | 54.1 | 53.7 | 48.1 | 51.3 | 52.0 | — | 58.9 |
| | (2.6) | (3.5) | (2.1) | (2.4) | (2.9) | (3.0) | (4.5) | (7.0) | — | (2.0) |

* For recency discrimination, stimulus-test interval defines the position of the more recent item of the stimulus pairs. Results are expressed as mean percentage correct with the SEM in brackets.

Post hoc planned comparisons showed the G × T interaction to be due to a selective deficit in recency discrimination in the PD group. Thus PD patients did not differ from control subjects in content recognition ($U = 74$, $P > 0.1$) but were impaired in recency discrimination ($U = 45$, $P < 0.02$), whereas patients with AD were impaired in both types of task (for content, $U = 38$, $P < 0.002$; for recency, $U = 28.5$, $P < 0.002$).

### *Effect of stimulus-test interval*

In statistical analysis of content recognition, stimulus-test interval defined the position of the appropriate single stimulus item. For recency discrimination, in which 2 stimuli are used, the stimulus-test interval defined the position of the more recent item of the stimulus pairs.

In all groups, performance declined with increasing stimulus-test interval on the VTO test (Table 2, fig. 1; $F(7, 294) = 39.03$, $P < 0.001$); the interaction $T \times I$ was not significant. The subject groups differed, however, in the relationship between test performance and stimulus-test interval; thus the interaction $G \times I$ was significant ($F(14, 294) = 1.93$, $P = 0.02$). Mean scores for each interval are shown in Table 2 and for pooled intervals in fig. 1. Patients with AD showed performance inferior to that of control subjects in both content recognition and recency discrimination at all stimulus-test intervals (for content recognition, $U = 38$, $P < 0.002$; for recency discrimination, $U = 28.5$, $P < 0.002$). The forgetting curves of the AD group were in general parallel but inferior to those of the control group. The PD group, by contrast, showed a pattern of performance in which disproportionately severe deficits were seen at the shorter stimulus-test intervals. Content recognition by the PD group was inferior to that by the control group at stimulus-test intervals of one ($U = 60$, $P < 0.05$) and three ($U = 64.5$, $P < 0.05$) but not at longer intervals and, unlike the control and AD groups, there was no decrement in performance between stimulus-test intervals of 1 and 6 (for controls, $T = 0$, $P < 0.02$; for AD, $T = 1$, $P < 0.05$; for PD, n.s.). At a stimulus-test interval

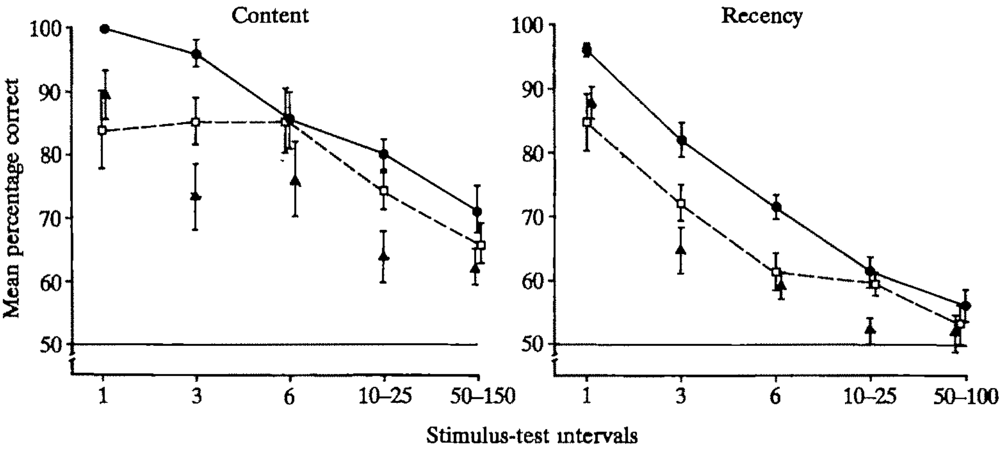

FIG. 1. VTO test performance related to the interval between stimulus and test (mean ± SEM). For recency discrimination, stimulus-test interval defines the position of the more recent item of the stimulus pairs. Unlike AD patients, PD patients showed defective content recognition only at the shortest stimulus-test intervals. Control (●——●); PD (□--□); AD (▲ . . . ▲).

of 1, the scores of the AD and PD groups did not differ although the PD group tended to inferior performance (PD 84%; AD 89%).

In recency discrimination, the groups as a whole did not differ significantly in the relationship of test performance to stimulus-test interval.

### *Relationship to dementia and minimental state test scores*

Exclusion of the 3 PD patients who were demented by DSM III criteria did not alter the qualitative differences between groups. The scores for the remaining 12 PD patients expressed as mean percentage correct, with SD in brackets, were as follows: total content 78.5 (9.96), total recency 64.0 (5.96); content at stimulus-test intervals of 1, 90.0 (18.1); of 3, 86.7 (13.0); of 6, 90.0 (16.0); of 10–25, 73.9 (12.4); and of 50–150, 69.5 (10.1).

The groups were divided according to their score on the memory and information section of the Blessed Dementia Scale (BDS) on which normal control subjects scored a maximum of 2. The total PD group was divided into Group 1 with normal BDS scores (0–2) and Group 2 with abnormal BDS scores (3–12), which included the 3 PD patients who were demented according to DSM III criteria. The AD group was divided into a mildly demented subgroup that matched the PD Group 2 for BDS score (3–12) and a moderately demented subgroup (BDS > 12) for which no parallel existed among the PD patients, owing to the overall greater severity of dementia in AD.

Within patient groups, scores on content recognition and recency discrimination tended to be lower in subjects with higher BDS scores (fig. 2). The relationship between performance and BDS score was similar in the 2 patient groups for content recognition but differed for recency discrimination. For content recognition, the correlations between test score and BDS score were not significant in either group (for PD, $r = -0.45$; for AD, $r = -0.30$). For recency discrimination, however, PD patients with higher BDS scores achieved significantly lower scores on the VTO test ($r = -0.84$, $P < 0.001$). In AD, the correlation between recency discrimination performance and BDS score was not significant ($r = -0.18$).

When performance was analysed according to stimulus-test interval, the PD subgroups showed a qualitatively similar pattern of performance to the total PD group (fig. 2). In general, however, the results were no longer significant, possibly because of the smaller number of subjects in each subgroup. In content recognition, scores of PD Group 1 tended to be inferior to those of control subjects at stimulus-test intervals of 1 ($U = 37.5$) but not at longer intervals. At the shortest interval of 1, PD Group 1 patients produced results equivalent to those of the mildly demented AD group but, at longer intervals, tended to superior performance ($U = 30.0$–$41.0$). PD Group 2 tended to inferior performance to the mildly demented AD group at a stimulus-test interval of 1 ($U = 29.5$) but did not differ at longer intervals. In recency discrimination, PD Group 2 achieved scores inferior to the mildly demented AD group only at a stimulus-test interval of 1 ($U = 21$, $P < 0.05$, one-tailed). At this point, the performance of PD Group 2 matched that of the more severely demented AD group, whereas the mildly demented AD group achieved scores equivalent to those of control subjects. At longer intervals, the scores of PD Group 2 did not differ from those of the mildly demented AD group but were superior to those of the moderately demented AD group.

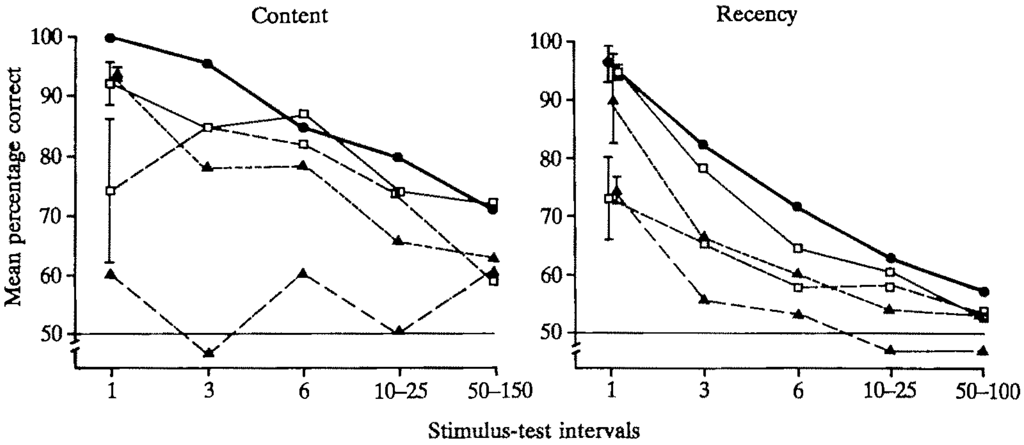

FIG 2. VTO test performance (mean ± SEM) across stimulus-test intervals related to the severity of dementia. For recency discrimination, stimulus-test interval defines the position of the more recent item of the stimulus pairs. In both tasks, more demented patients showed inferior performance but PD patients performed disproportionately poorly at short stimulus-test intervals. Control, n = 15 (●——●); PD, n = 8, BDS = 0–2 (□——□), PD, n = 7, BDS = 3–12 (□---□); AD, n = 13, BDS = 3–12 (▲---▲); AD, n = 2, BDS = 13+(▲-·-▲)

### *Interstimulus interval in recency discrimination*

The effect on recency discrimination of increasing intervals between items of the stimulus pair was analysed as follows. The position of the more *recent* of the two items was defined by its position relative to the test, that is, as 1, 3, 6, 10, . . . items prior to test; for each of these positions, an ANOVA was performed of Group × Interval × Test where Interval refers to the number of items between the more *remote* stimulus and test. There were significant effects on Interval for all positions of the more recent stimulus (for positions 1, 6 and 15, $P < 0.001$; for positions 3 and 10, $P < 0.01$). There were no significant G × I interactions. Thus in all groups, recency discrimination was better with longer intervals between items of a stimulus pair.

## DISCUSSION

The purpose of this study was to examine the relationship between content recognition memory and recency discrimination in PD and AD as a function of the interval between stimulus and test. The main findings were (1) patients with AD were impaired in all tasks at all retention intervals; (2) unlike patients with AD, patients with PD had a deficit in verbal recency discrimination with preserved recognition of stimulus content; and (3) patients with PD showed selective or disproportionate deficits in content recognition at the shortest stimulus-test intervals, unlike AD patients whose forgetting curves were below but parallel to those of control subjects at all stimulus-test intervals. These results suggest specific cognitive deficits in verbal recency discrimination and in short-term memory processing in PD.

These cognitive deficits occurred in a group of patients who were not preselected by any behavioural criterion and who were thus representative of a typical outpatient group of PD patients. Only 3 of the 15 cases were demented by DSM III criteria, a proportion representative of the PD population in general (Mortimer *et al.*, 1985). The results cannot be attributed to the nonspecific effects of Alzheimer-type dementia because the qualitative nature of the findings is not altered by exclusion of these cases, even assuming that their dementia is of the Alzheimer type. More specifically, the findings of *qualitatively* different results in a control AD group essentially excludes this possibility. Equally, the results cannot be considered as artefacts resulting from the motor disorder or poor attentional skills because these deficits would tend to affect performance indiscriminately, whereas our results show selective deficits among cognitive processes examined under parallel conditions. Parkinson's disease and Alzheimer's disease share many cognitive deficits and, in some respects, differ quantitatively but not qualitatively (S. Corkin, J. H. Growden and M. J. Nissen, unpublished observations; Mayeux and Stern, 1983). In this study, however, poor temporal ordering and impaired short-term memory processing were features that distinguished both qualitatively and quantitatively the cognitive decline of PD from that of AD.

### *Verbal recency deficits in PD*

Studies of normal subjects and patients with memory disorders have indicated that recency discrimination is not slavishly linked to content recognition. Evidence from normal subjects suggests that these two cognitive functions are dissociable and are affected differentially by alterations in the learning strategy (Hasher and Zacks, 1979). Thus performance on recognition memory tasks was better if subjects were given prior instructions to learn the test material (intentional or effortful learning) than if learning took place without instruction, as an incidental accompaniment to some other task, such as reading (incidental or automatic learning). Recency discrimination, by contrast, was not affected by a change from incidental to intentional learning. Studies of some amnesic patients have shown loss of temporal contextual memory in the absence of deficits in recognition memory; this loss has been postulated to form the basis of the amnesic syndrome (Huppert and Piercy, 1976; Hirst and Volpe, 1982; Schacter *et al.*, 1984). Squire *et al.* (1981) have suggested that this pattern of performance in amnesia is a simple consequence of degraded normal memory because recency discrimination, being a more difficult task, is more susceptible to disruption by disease than is content recognition. Even when normal memory was degraded to the amnesic level, however, patients with

Korsakoff's syndrome still performed more poorly in recency discrimination than did a control group (Meudell *et al.*, 1985). Moreover, in the severely amnesic patient, H.M., the reverse pattern occurred: H.M. showed preserved recency discrimination under conditions where recognition performance was at chance levels and in no circumstance was recency discrimination impaired when recognition memory was normal (Sagar *et al.*, 1984). In studies of epileptic patients treated by focal cortical excision, Milner and colleagues have demonstrated dissociations of function dependent upon lesion site: frontal excisions are associated with impaired recency discrimination and intact recognition memory whereas temporal excisions are followed by recognition deficits but preserved recency discrimination (Milner, 1971, 1974; Corsi, 1972). Taken together, these observations suggest that content recognition and recency discrimination are, under certain circumstances, independent cognitive processes that may be selectively disrupted or manipulated.

In the present study, patients with PD showed recency discrimination deficits when content recognition was preserved. The interaction Group × Task was significant, indicating that the groups differed in their relative performance on the tasks of content recognition and recency discrimination. This interaction cannot be attributed to ceiling effects at short intervals on content recognition because, at short intervals, the difference between groups is greatest. Equally, the results cannot be due to floor effects in recency discrimination at long intervals because such effects would reduce rather than increase the interaction. Instead, the significant Group × Task interaction reflected the observations that content recognition by the PD group was as good overall as that of the control group but its recency performance was as poor as that of the AD patients, who were impaired on both tasks. Furthermore, recency discrimination in PD showed a different relationship to score on a minimental state test, the BDS, from either recency discrimination in AD or content recognition in either group. These observations suggest that recency discrimination in PD is also a specific deficit and not a simple consequence of impaired memory for content, although further studies will be needed to clarify this point.

In concurrent studies we have shown that, compared with AD patients, patients with PD have a disproportionately severe deficit in their ability to date past historical events when account is taken of their relatively preserved recognition of the content of these events; we have postulated frontal lobe dysfunction as the basis of the impairment (Sagar *et al.*, 1985*a*; 1988). The present study demonstrated that PD patients also have verbal recency discrimination deficits in new learning despite preserved content recognition, suggesting that impaired dating capacity may be partly based upon an impaired ability to make temporal discriminations. Several studies suggest that recency discrimination is dependent upon the integrity of the frontal lobes, whereas recognition memory is served by structures in temporal and diencephalic regions (Milner, 1971, 1974; Corsi, 1972; Schacter *et al.*, 1984; Mayes *et al.*, 1985; Meudell *et al.*, 1985). Although the recency discrimination deficit in PD cannot be established absolutely as a specific deficit, the results of our two studies together suggest that patients with PD may have impaired dating capacity and poor temporal discrimination due to pathology in the frontal lobes or their connections. In further studies (Sullivan *et al.*, 1985; Sagar, 1987), we have shown that, compared with AD patients, PD patients are selectively impaired in their capacity to arrange pictures in sequence so as to tell a logical story, a task that is also dependent upon frontal lobe function (McFie and Thompson, 1972). These observations indicate that impaired dating and recency discrimination in PD may form part of a broader deficit in cognitive sequencing as a result of dysfunction in the frontal lobes. In all these studies, the deficits in the PD group were disproportionately severe when compared with performance of an AD group, indicating that these cognitive deficits cannot be explained solely by the presence of Alzheimer-type cognitive impairment in PD.

### *Deficits in short-term memory processing in PD*

Patients with PD were poor at content recognition and recency discrimination when tests of retention followed soon after presentation of the stimulus but showed less deficit or normal performance when the stimulus-test intervals were longer. This pattern was not seen in AD. The results cannot be explained by deficits in attention, perception or registration since an inadequately encoded stimulus would be poorly recognized whatever the stimulus-test interval. Equally, the findings cannot be due to factors, such as practice effects or improved attention, that may predictably improve performance as the testing proceeds, because the stimulus-test intervals were distributed randomly throughout the whole test. The special relationship of impairment to short stimulus-test intervals suggests that short-term memory processes in PD are impaired. We have considered two possible explanations for these results, bradyphrenia and inability to manipulate multiple items in PD.

*Bradyphrenia in PD.* The first hypothesis is that short-term memory processes in PD, although adequate, are slowed. Recognition tested during this period is poor because the material has been incompletely encoded but, after an interval, improves as registration increases. This cognitive slowing may be analogous to the slowing of movement or bradykinesia, which forms one of the cardinal motor signs of PD. Clinical descriptions have also drawn attention to hesitancy and slowing of cerebration in PD and, by analogy with motor function, have used the term bradyphrenia to catalogue these deficits (Naville, 1922). Wilson *et al.* (1980) have provided experimental support for this clinical concept by showing that scanning of short-term memory is slowed but accurate in PD and that the effects are not readily attributable to extreme reaction times. In another study (Rafal *et al.*, 1984), in which patients acted as their own controls, speed of short-term memory scanning was shown to be independent of motor function although no absolute level of function could be established in the PD group because of the lack of normal control subjects. Taylor *et al.* (1986) studied a selected group of PD patients deemed nondemented on clinical evaluation and found evidence of bradyphrenia on a block-counting task on which their accuracy was normal. Rogers *et al.* (1987) detected cognitive slowing on the digit-symbol substitution task in untreated PD patients; the deficit was related to structural brain disorder, mostly cerebral atrophy, on CT scans, and to the severity of associated depression. None of these studies incorporated a non-parkinsonian demented group to examine whether the pattern of performance in the PD group was different from the nonspecific effects of dementia. The results of our study are compatible with the notion that short-term memory processing is slowed but accurate in PD. An explanation based on slowing of cognitive processes would predict that PD patients would perform poorly on any memory task soon after registration of information, whether testing be conducted in recall or recognition format.

*Hypothesis: inability to manipulate multiple items in PD.* The second possible explanation of the short-term memory deficit lies in dysfunction of a higher-order memory system, based upon the frontal lobes, that is capable of manipulating, discriminating and comparing independent memoranda (Warrington and Weiskrantz, 1982; Baddeley, 1985; Warrington, 1985; Baddeley and Wilson, 1986). Deficits in this cognitive mediational system were proposed as the basis of the selective dating impairment in our studies of remote memory function in PD (Sagar *et al.*, 1985*a*, 1988). Such a system could serve recency discrimination and cognitive sequencing tasks, which PD patients also perform poorly (Sullivan *et al.*, 1985; Sagar, 1987; Sagar and Sullivan, 1988) and may be operative in manipulating multiple items of any nature, whether mnemonic or nonmnemonic. Dysfunction of the same system could underlie the clinical phenomenon of bradyphrenia if certain assumptions are fulfilled: (1) that at the short but not long stimulus-test intervals, stimuli are within a short-term memory store; (2) that the foils, being common nouns, form part of the subjects' long-term memory store; and (3) that comparison of memoranda across stores is more difficult than within the same store. If these conditions are fulfilled, then impoverished performance may be most marked at short stimulus-test intervals owing to the particular incapacity in discriminating, in a two-choice recognition task, between stimuli in different memory stores. Such a model would not require slowing of cognitive processes but the deficits would nevertheless be manifest clinically as slowness in producing accurate responses.

In so far as discrimination between stimuli in different memory stores demands shifting of attention from one cognitive process to another, the impairment may be related to deficits on other tasks in which subjects make attentional shifts between multiple items. Specifically, patients with PD show difficulty in altering cognitive attitude in response to changing environmental demand, a process known as 'set-shifting' (Lees and Smith, 1983; Cools *et al.*, 1984). Although this term is traditionally applied to attentional shifting between different stimulus characteristics, similar attentional shifts may also take place between different cognitive processes. Although speculative, these considerations suggest that the results of this study may be explained by dysfunction of processes that are also involved in classical set-shifting. Both the cognitive mediational system and processes serving set-shifting are considered to depend on integrity of the frontal lobes, raising the possibility that bradyphrenia may also arise from frontal lobe dysfunction. This hypothesis predicts that patients with PD would show a general impairment in performing multiple tasks simultaneously, a deficit that may extend to mnemonic and nonmnemonic cognitive processes and may also involve motor control.

The lack of similar findings in AD indicates that the short-term memory deficits of the PD group are not attributable simply to nonspecific effects of Alzheimer-type dementia. Rather, the results of this study support the concept of bradyphrenia as a specific clinical finding in PD, although the underlying cognitive deficits need not involve prolonged processing time.

### *Frontal lobe dysfunction in PD*

A number of cognitive deficits have been claimed to be characteristic of PD (Sagar, 1985; Growdon and Corkin, 1986; Sagar and Sullivan, 1988). The impaired capacities include visuospatial function (Boller *et al.*, 1984); motor sequencing and predictive behaviour (Flowers, 1978; Stern *et al.*, 1983), dating capacity (Sagar *et al.*, 1985*a*, 1988), verbal recency discrimination (Sagar *et al.*, 1985*b*, this study), cognitive sequencing (Sullivan *et al.*, 1985; Sagar, 1987; Sagar and Sullivan, 1988) and processes underlying the clinical phenomenon of bradyphrenia (Naville, 1922; Wilson *et al.*, 1980; Sagar *et al.*, 1985*b*, this study). Many of these deficits can be attributed to frontal lobe dysfunction. Other workers have provided evidence of impairment in patients with PD on tests traditionally associated with frontal lobe function including release from proactive interference (Tweedy *et al.*, 1982), double simultaneous motor acts (Schwab *et al.*, 1954) and the Wisconsin Card Sorting Test (Lees and Smith, 1983). These observations suggest that frontal lobe dysfunction may form a large contribution to the aetiology of cognitive impairment in PD. For some of these deficits, the lack of equivalent findings in AD indicates that the frontal lobe pathology must be quantitatively or qualitatively different from that in AD. Normal brain has a richness of subcortical-cortical interconnections that are disrupted in both AD and PD. Although multiple neurotransmitter systems are affected in both diseases, PD differs from AD in the extent of loss of dopaminergic subcortical-cortical projections (Thierry *et al.*, 1978). In PD, the cholinergic deficits are usually milder than in AD (Perry *et al.*, 1985). Loss of noradrenergic cells of the locus coeruleus occurs in both diseases (Bondareff *et al.*, 1982; Hornykiewicz, 1982). Cholinergic, dopaminergic and noradrenergic neurons project to the frontal cortex (reviewed by Sagar and Sullivan, 1988). Differential involvement of these subcortical-cortical neurotransmitter systems in AD and PD may account for the differing patterns of cognitive impairment in the two diseases and explain the selective loss of frontal lobe function in PD.

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# CRYOGLOBULINAEMIC NEUROPATHY

## A CLINICAL, MORPHOLOGICAL AND IMMUNOCYTOCHEMICAL STUDY OF 8 CASES

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## SUMMARY

Clinical, pathological and immunocytochemical studies are described for 8 patients with cryoglobulinaemia and peripheral neuropathy: 5 had essential cryoglobulinaemia and 3 secondary cryoglobulinaemia. The cryoglobulins in 2 cases were type II (mixed cryoglobulins with a monoclonal component), type III (mixed polyclonal cryoglobulins) in 2 others, and were not characterized in 4. In all patients the neuropathy had an acute or subacute onset and in 7 it was initially asymmetric but, during the illness, in 3 it gradually progressed to a symmetric sensorimotor polyneuropathy. All patients had sural nerve biopsies. In 4 there was widespread vasculitis with necrosis of vessel walls and perivascular inflammatory cells. In another 2, thickening of vessel walls and luminal narrowing without inflammatory cell infiltration, together with loss of myelinated fibres from single fascicles or focally within fascicles, suggested that the neuropathy was of vascular origin. In all patients the main pathological damage was axonal degeneration. Signs of axonal regeneration were rare. The total number of myelinated fibres was reduced in all cases, from 24 to 95% below the lower limit of normal control values. Large diameter fibres were lost preferentially in 7 patients, being below 16.5% of the total number.

Several possible pathogenetic mechanisms have been suggested for cryoglobulinaemic neuropathy, including immunologically mediated demyelination and ischaemic injury due to intravascular deposits of cryoglobulins or vasculitis. Our observations therefore confirm a major role for ischaemic factors, secondary to inflammatory vascular destruction, in the pathogenesis of peripheral neuropathy in most cases of types II and III cryoglobulinaemia.

## INTRODUCTION

Peripheral neuropathy associated with cryoglobulinaemia has been described by several investigators but the relationship of the abnormal protein to the neurological manifestations is still uncertain. Ischaemic factors related to thrombosis or increased blood viscosity, immunologically mediated damage, and cellular infiltration, have all been proposed as being involved in the pathogenesis of cryoglobulinaemic disease (McLeod *et al.*, 1984). We have studied 8 patients with

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cryoglobulinaemic neuropathy clinically, pathologically and immunocytochemically, to obtain additional information as to the pathogenic mechanisms responsible for nerve damage.

## PATIENTS AND METHODS

Eight patients with cryoglobulinaemia and peripheral neuropathy were studied. Their ages ranged from 34 to 83 yrs. Five had essential cryoglobulinaemia and in the remaining 3 (Cases 2, 3, 4) it was associated with scleroderma, chronic active hepatitis and rheumatoid arthritis. The clinical features of the 8 patients at the time they were admitted to hospital are summarized in Table 1. There were no differences in the time course and severity of neuropathy in the 8 subjects At the time of onset, all but 1 (Case 1) had an asymmetric sensorimotor neuropathy; Cases 4, 6 and 8 subsequently developed a symmetric polyneuropathy. The initial appearance of the neuropathy was acute in 6 subjects and subacute in the other 2 (Cases 1, 4). The patients had marked weakness, especially in the distal muscles of the legs and less frequently in the arms (Cases 2, 4, 8) and thighs (Cases 1, 2, 8). The tendon reflexes were absent or depressed in the lower limbs in all cases and in the upper limbs in 2 cases. There were paraesthesiae and sensory loss in the feet in all cases. There was no cerebral or cranial nerve involvement.

TABLE 1 CLINICAL CHARACTERISTICS OF PATIENTS WITH CRYOGLOBULINAEMIC NEUROPATHY

| *Case/ age (yrs)/sex* | *Presentation at onset* | *Distal weakness* | *Proximal weakness* | *Absent or depressed tendon reflexes* | *Paraesthesiae* | *Sensory loss* | *Degree* |
|---|---|---|---|---|---|---|---|
| 1/83/M | S, PN | L | L | L | — | U, L | Severe |
| 2/42/F | A, MN | U. L | L | L | L | L | Severe |
| 3/34M | A, MN | L | — | L | L | L | Moderate |
| 4/48/M | S, MN | U, L | — | U, L | U, L | U, L | Severe |
| 5/52/M | A, MN | L | — | L | L | L | Severe |
| 6/53/M | A, MN | L | — | L | L | L | Moderate |
| 7/54/M | A, MN | L | — | L | L | L | Moderate |
| 8/56/M | A, MN | U, L | L | U, L | L | L | Moderate |

A = acute; S = subacute; PN = polyneuropathy; MN = mononeuropathy; U = upper limbs; L = lower limbs.

All patients received prednisone alone. One patient (Case 7) improved with treatment. Another (Case 4), who initially improved with treatment, subsequently showed remissions and exacerbations, the latter temporally related to reductions in medication. Six patients did not improve with treatment; 2 of these 6 (Cases 2, 3) died at 20 and 36 months, respectively, after the beginning of the primary disease.

In 4 cases, the precipitate was characterized according to Brouet *et al.* (1974), and the cryoglobulins were classified as type III (IgM-IgG) for Cases 4 and 6, and as type II (IgM-IgG) for Cases 7 (monoclonal IgM with kappa light chain) and 8 (monoclonal IgM with lambda light chain).

The ESR was normal for 6 of the 8 patients. Other acute phase reactants (C-reactive protein, mucoproteins, alpha$_2$-globulins) and rheumatoid factor were abnormal in all cases. The 'cryocrits' (percentage of cryoprecipitate in total serum) of the 8 subjects ranged from 2 to 13%. After serum immunoelectrophoresis at 37° C, an IgM peak was found in the 2 patients with type II cryoglobulins.

The protein content of the CSF was increased in only 1 patient (Case 2). CSF cell counts were normal.

Cutaneous manifestations, such as skin ulcers, ecchymoses, erythematous patches and purpura, especially in the lower limbs, were seen in 7 patients (Cases 1-7), 3 of whom had secondary cryoglobulinaemia. Skin biopsies showed leukocytoclastic vasculitis. Case 8 had glomerulonephritis and anaemia due to circulating cryoagglutinin. None of the patients studied had a familial neuropathy. Malignancy, amyloidosis and other causes for neuropathy, such as diabetes mellitus, neurotoxins or porphyria, were excluded.

Electrophysiological studies were performed in 6 (Cases 1-5, 7) of the 8 patients. Ulnar and deep peroneal motor nerve conduction velocities and the median and sural nerve sensory nerve action potentials were measured. Stimulation and recording were performed with surface electrodes. Skin temperature was maintained at 36° C by a thermostat driving a heating lamp. The EMG in the arms (concentric needle electrode recordings) was normal or showed only mild signs of distal denervation. In the distal muscles of the legs, moderate fibrillation and a reduced motor unit recruitment pattern at full effort were observed in some cases. There was an increase in polyphasic potentials in all 6 cases. Frequently, at the onset of the neuropathy, the severity of the EMG alterations was asymmetric. Deep peroneal motor nerve conduction velocity was slowed in 5 (Cases 2-5, 7) of the 6 patients investigated. There were no evoked sensory action potentials in either sural nerve in 4 patients and amplitude was reduced in 2 (Cases 1, 7). Nerve conduction parameters for the median and ulnar nerves were less frequently altered (Table 2). Sural nerve biopsies were taken just proximal to the lateral malleolus in each patient. They were fascicular in 2 patients (Cases 6, 7) and total in the others. Segments from each nerve were fixed in 10% formalin, embedded in paraffin, and sections from different sites in each specimen were stained with haematoxylin and eosin, Congo red, and Weigert's stain for elastic fibres. Some paraffin sections were prepared for the PAP method for immunocytochemical staining. Other nerve fragments were immediately fixed by immersion in buffered 1% osmium tetroxide. After alcohol dehydration, they were embedded in Epon. Semithin transverse sections were stained with toluidine blue and examined under the light microscope to estimate the distribution and severity of myelinated fibre abnormalities. The numbers and diameters of myelinated fibres were measured from micrographs of 2 or 3 fascicles for each

TABLE 2 NERVE CONDUCTION STUDIES

| | *Case* | | | | | | |
|---|---|---|---|---|---|---|---|
| | *1* | *2* | *3* | *4* | *5* | *7* | *Normal values (mean ± SD)* |
| Ulnar MNCV (m·s$^{-1}$) (elbow-wrist) | 53.8 | 33.5 | 55.3 | 53.3 | 47.4 | 52.2 | 62.2±3.8 |
| DML (ms) | 3.0 | 4.7 | 2.9 | 3.4 | 3.9 | 2.3 | 2.8±0.3 |
| Amplitude (mV) | 15.0 | 7.0 | 16.0 | 11.0 | 10.0 | 10.0 | 28.1±4.1 |
| Deep peroneal MNCV (m·s$^{-1}$) (knee-ankle) | 48.2 | 28.1 | 43.7 | 18.3 | 19.2 | 40.2 | 50.4±3.6 |
| DML (ms) | 4.0 | 8.2 | 6.0 | 10.2 | 11.1 | 4.6 | 4.3±0.5 |
| Amplitude (mV) | 6.5 | 1.5 | 1.0 | 0.5 | 0.8 | 6.0 | 9.1±3.6 |
| Median SNCV (m·s$^{-1}$) (wrist-digit II) | 48.1 | 33.4 | 55.1 | — | 39.1 | 54.2 | 55.1±5.3 |
| Amplitude ($\mu$V) | 10 | 5 | 18 | Absent | 4 | 16 | > 12 |
| Sural SNCV (m·s$^{-1}$) (calf-malleolus) | 44.2 | — | — | — | — | 44.8 | 48.5±3.7 |
| Amplitude ($\mu$V) | 4 | Absent | Absent | Absent | Absent | 2 | > 9 |

patient and the results were compared with control data in the literature (Behse and Buchthal, 1978). Ultrathin transverse sections were made on a Reichert ultramicrotome, stained with uranyl acetate and lead citrate, and examined under a Zeiss electron microscope.

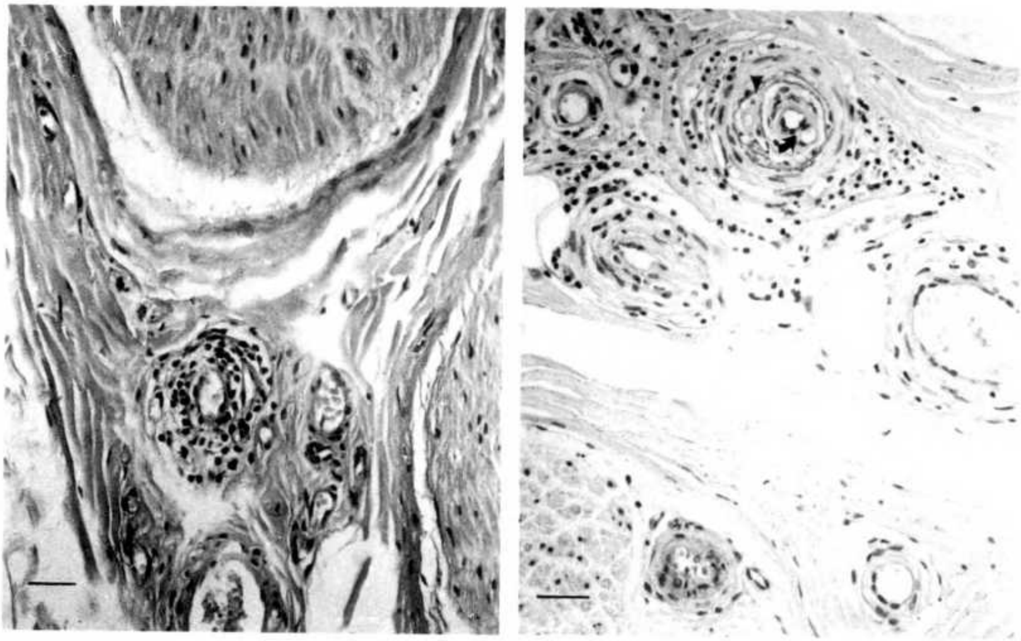

FIG. 1 (*left*). Transverse section of sural nerve (*Case 7*). Vasculitis of a small-sized artery in the epineurium; inflammatory infiltration of the vessel wall and perivascular space is present. Paraffin-embedded section, haematoxylin and eosin. Bar = 50 μm.

FIG. 2 (*right*). Transverse section of sural nerve (*Case 3*). Perivascular inflammatory infiltration surrounds an epineurial artery; the internal lamina appears irregular and partly disrupted by oedema (arrow head). The occluded lumen has been recanalized (arrow). Paraffin-embedded section, Weigert's stain. Bar = 50 μm.

## RESULTS

In Cases 3, 5, 7 and 8, light microscopic examination of transverse sections of paraffin-embedded sural nerve showed widespread vasculitis affecting medium and small-sized arteries in the epineurium. The inflammatory cell infiltrates in the vessel walls and perivascular space (fig. 1) consisted mostly of lymphocytes and monocytes, but in Case 5 there were also polymorphonuclear cells. Sometimes the perineurium of some fascicles was involved by inflammatory infiltrates, but only infrequently were a few lymphocytes seen around small endoneurial vessels, even in cases with widespread vasculitis. With Weigert's stain for elastic fibres, the internal lamina of the arteries appeared irregular and sometimes partly disrupted by oedema (fig. 2). With the PAS stain, the basal membranes of affected vessels were often increased in thickness. The occluded lumina of some severely damaged arterioles were recanalized (fig. 2). Other vascular abnormalities, such as hyperplasia of muscular and endothelial cell layers, were noted. In the nerves of Cases 4 and 6, in which no inflammatory infiltration could be seen, there was thickening of the vessel walls and luminal narrowing produced by fibrous tissue and swollen endothelial cells. There was no evidence of amyloid deposition in any of the nerves. By the PAP method, some endoneurial vessel walls of 2 patients (Cases 4, 5) showed positive immunostaining with IgM and IgG antisera (fig. 3). The perineurium was also slightly immunostained, but epineurial vessels were negative. There were no IgM or IgG deposits on myelin sheaths, axons or endoneurial connective tissue. In no instance did the serum of any patient immunostain the endoneurial vessels or other structures of normal human nerve.

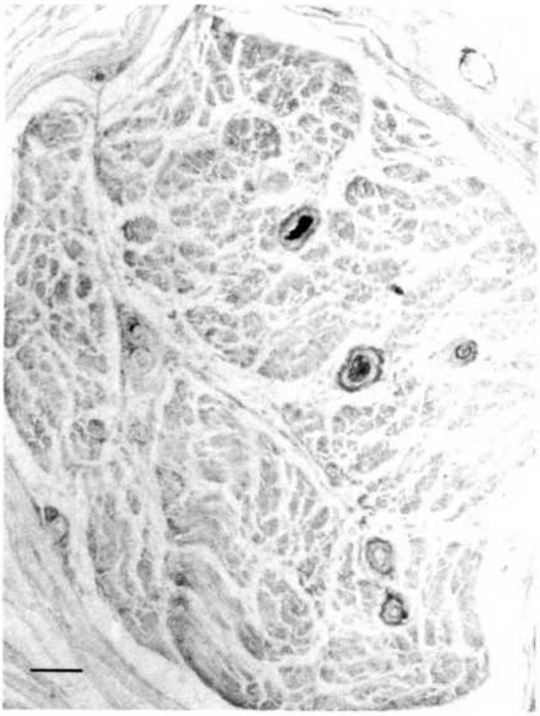

FIG. 3. Transverse section of sural nerve (*Case 5*). Some endoneurial vessel walls show positive immunostaining with IgM antisera. Paraffin-embedded section, PAP method. Bar = 50 $\mu$m.

In transverse semithin sections, myelinated nerve fibre density was variably diminished. In Cases 2, 3, 7 and 8, some fascicles had greater myelinated fibre loss than others; sometimes (Cases 4, 6) this was particularly evident centrally within fascicles (fig. 4). Myelin ovoids, indicating acute axonal degeneration, were observed in all 8 biopsies; in Cases 2, 3, 7 and 8 they were numerous. In Cases 2, 3, 7 and 8 occasional axons were surrounded by thin myelin sheaths. No signs of acute demyelination were encountered. The amount of endoneurial connective tissue was increased in all nerves and was especially abundant in Cases 3, 4, 5, 6 and 7, in which myelin fibre depletion was marked.

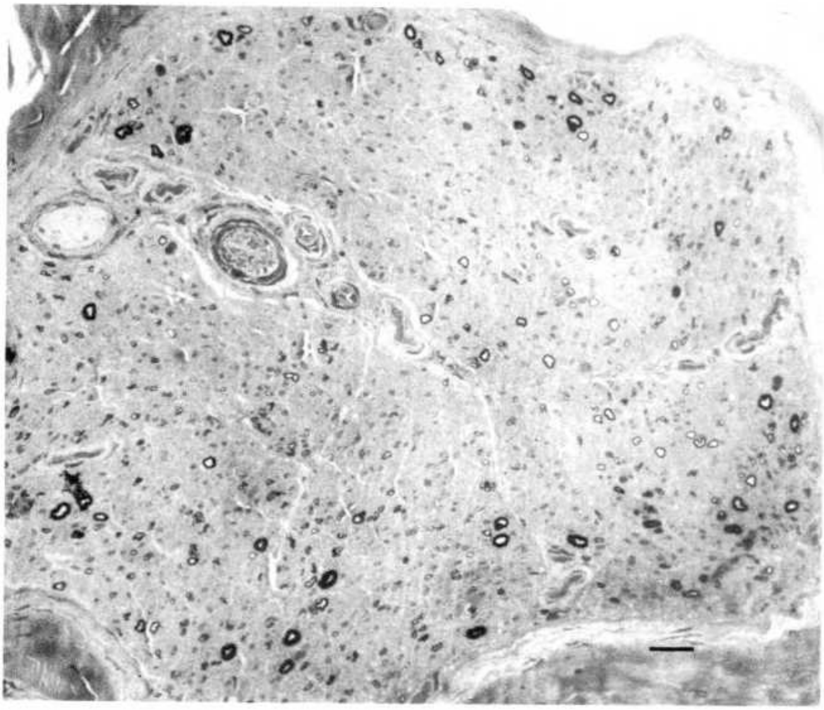

FIG. 4. Transverse section of sural nerve (*Case 4*). The myelinated fibre loss is particularly evident in the centre of the fascicle. Epon-embedded semithin section, toluidine blue. Bar = 50 μm.

For morphometric analyses (Table 3), the total endoneurial area ranged from 0.73 to 1.21 mm², excluding the fascicular biopsies. Except for Case 1, the density of myelinated fibres was reduced in all patients and it was particularly low in Case 5. This case showed the most severe loss of myelinated fibres, which were decreased to 95% below the lower limit of normal control values. In the other cases, the total number of myelinated fibres was reduced from 23.8 to 86.5% below the

TABLE 3. CRYOGLOBULINAEMIC NEUROPATHY: HISTOMETRY

| *Case* | *No. myelinated fibres* | *Density of myelinated fibres* | *Myelinated fibres > 8 μm (%)* | *No. of clusters* | *Endoneurial area (mm²)* |
|---|---|---|---|---|---|
| 1 | 4115 | 5637 | 13.4 | 95 | 0.73 |
| 2 | 2750 | 2371 | 8.4 | 26 | 1.16 |
| 3 | 1499 | 1239 | 11.0 | 12 | 1.21 |
| 4 | 702 | 798 | — | — | 0.88 |
| 5 | 256 | 316 | 5.8 | — | 0.81 |
| 6* |  | 2453 | 33.7 |  |  |
| 7* |  | 2306 | 9.4 |  |  |
| 8 | 3883 | 5178 | 16.5 | 6 | 0.75 |
| Controls** | 5200–9500 | 5400–8600 | 22.8–34.6 | < 38 | 0.65–1.26 |

* Fascicular biopsy. ** Range from Behse and Buchthal (1978).

lower normal limit. Large diameter fibres were lost preferentially in all cases but 1 (Case 6). Clusters of thinly myelinated fibres, a sign of regeneration after axon degeneration, were increased over the normal value only in Case 1.

Ultrastructural examination of the sural nerve biopsies confirmed that the main type of damage in all cases was axonal degeneration. In only 2 biopsies (Cases 4, 5) were unmyelinated fibres affected: most were degenerating, and many denervated Schwann cell processes were present. In 6 patients (Cases 3–8) there were ultrastructural alterations in capillaries and small endoneurial vessels. The endothelial cells were hypertrophied, with processes that almost completely occluded the lumen (figs 5, 6). Some of them had long branched cytoplasmic projections. These projections were often vacuolated. The basal lamina at the outer surface of the endothelial cells was sometimes discontinuous, increased in thickness, and reduplicated.

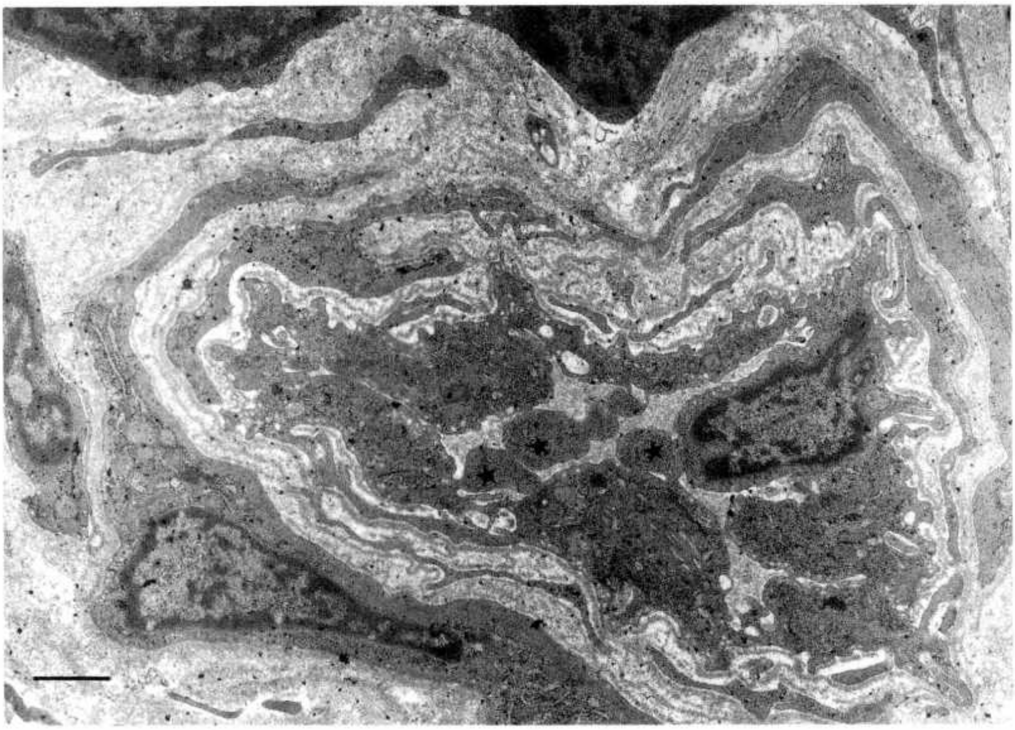

FIG. 5. Endoneurial capillary (*Case 5*). Electron micrograph showing hypertrophic endothelial cells with pseudopodia (★) almost completely occluding the lumen. Bar = 1 μm.

## DISCUSSION

It is assumed that there are two main mechanisms responsible for the clinical findings that we have observed in patients with cryoglobulinaemia (Brouet *et al.*, 1974): intravascular deposition of cryoprotein and/or vasculitis due to circulating immune complexes. A third mechanism is related to possible autoantibody activity by the cryoglobulin (Clemmensen *et al.*, 1986). These three mechanisms may be considered to have been potentially implicated to explain the pathogenesis of cryoglobulinaemic neuropathy. Some studies on nerve involvement in cryoglobulinaemia have been published, but in only 8 instances have the pathological alterations been documentated by nerve biopsy (Siguier *et al.*, 1964; Dayan and Lewis, 1966; Cream *et al.*, 1974; Betourné *et al.*, 1980; Vallat *et al.*, 1980; Chad *et al.*, 1982; Konishi *et al.*, 1982; Lippa *et al.*, 1986).

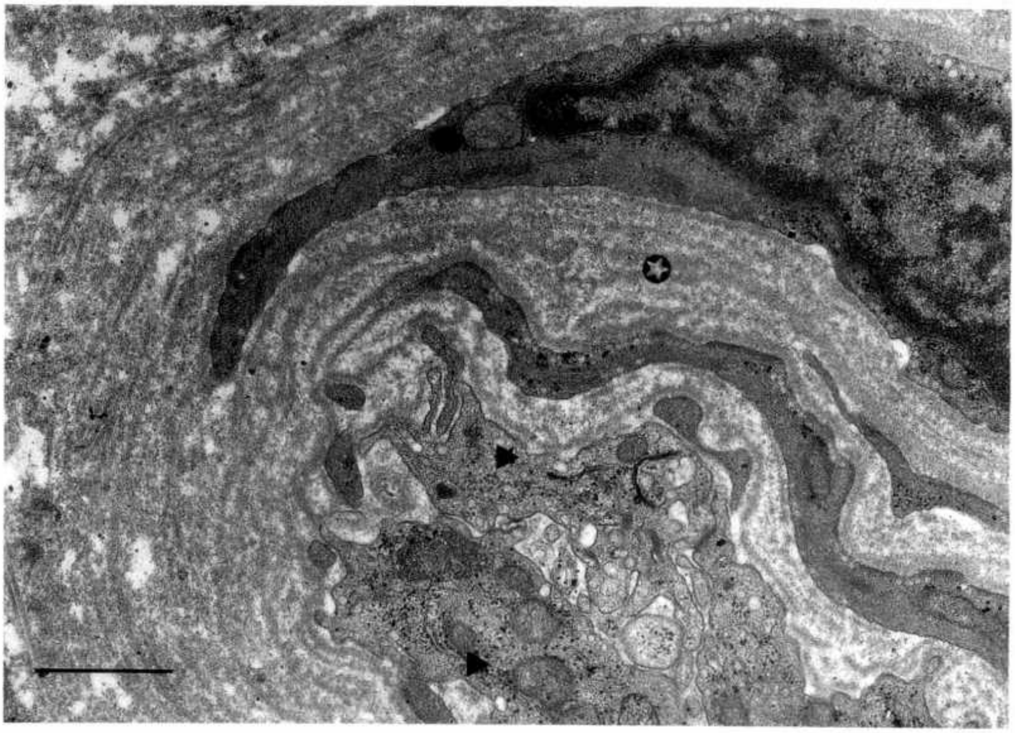

FIG. 6. Endoneurial capillary (*Case 8*). Electron micrograph showing that the basal lamina at the outer surface of the endothelial cells is increased in thickness (✪) and reduplicated. Endothelial cells are hypertrophied (▲). Bar = 1 μm.

Vasculitis of the vasa nervorum was considered to be responsible for nerve damage in a case of mixed cryoglobulinaemia reported by Cream *et al.* (1974). On nerve biopsy, they found lymphocytic and plasma cell infiltration extending through the perineurium into the nerve fascicle, together with alterations in the internal elastic lamina and signs of revascularization in an epineurial artery. Konishi *et al.* (1982) described a patient with mononeuritis multiplex with mixed cryoglobulinaemia. Their study of the nerve pathology revealed vasculitis, with the perineurium of most of the nerve fascicles affected by inflammatory and fibrous changes. Chad *et al.* (1982) reported a woman with vasculitic neuropathy and essential mixed cryoglobulinaemia.

Demyelination as a possible mechanism of cryoglobulinaemic neuropathy has been proposed by some investigators (Siguier *et al.*, 1964; Dayan and Lewis, 1966). Betourné *et al.* (1980) reported a demyelinating neuropathy related to type III cryoglobulinaemia that improved after plasma exchange. Clemmensen *et al.* (1986) have recently described a patient with an IgM lambda monoclonal essential cryoglobulinaemia that showed autoantibody activity with specificity for type I collagen. Farivar *et al.* (1976) demonstrated intravascular deposits of cryoglobulins in the intima of small arteries of the gastrocnemius muscle by immunofluorescence techniques in a patient with chronic hepatitis and peripheral neuropathy. They suggested that intravascular deposition of the cryoproteins can cause ischaemic injury to nerves by interfering with the local microcirculation. The presence of cryoglobulin masses with a tubular configuration in the walls and lumina of some vasa nervorum and in the endoneurial space in a patient with monoclonal cryoglobulinaemia and neuropathy was also documented by electron microscopy (Vallat *et al.*, 1980).

We have described 8 patients with peripheral neuropathy associated with type II or type III cryoglobulinaemia. In most of our patients we found a multifocal neuropathy with an acute or subacute onset, which is generally considered to be the usual clinical presentation for vasculitic neuropathy. Seven patients presented the type of skin involvement usually described for systemic hypersensitivity angiitis. The relationship between mixed cryoglobulins and vasculitis of small or medium-sized vessels is widely recognized (Conn *et al.*, 1976; Weisman and Zvaifler, 1980). Logothetis *et al.* (1968) described a symmetric distribution of neurological deficits and cutaneous purpuric and ischaemic manifestations in a case of secondary cryoglobulinaemia, suggesting a common vascular aetiology.

Nerve biopsy of 4 of our patients showed vasculitis affecting the vasa nervorum and in 2 cases the centre of nerve fascicles was found to be severely damaged, supporting the hypothesis of an ischaemic basis, in accord with the observations of Dyck *et al.* (1972). Experimental data after arterial ligation (Hess *et al.*, 1979) and microsphere embolization (Nukada and Dyck, 1984) also confirmed this to be the characteristic pattern of nerve involvement in conditions of ischaemia.

Two of our patients, 1 with vascular alterations and 1 with frank vasculitis of the vasa nervorum, had deposits of IgM and IgG in the walls of some endoneurial vessels. The presence of immunoglobulins in endoneurial vessel walls may represent entrapped immune complexes along the vascular basement membrane during a state of increased permeability. The integrity of this filtration barrier is lost when inflammatory changes develop (Cochrane, 1971; Gower *et al.*, 1977). In their studies, Clemmensen *et al.* (1986) found a similar location of the IgM monoclonal cryoglobulin in the adventitia and media of intramuscular vessels. In both our patients with immunoglobulin deposition, only the endoneurial vessels were involved, the epineurial vessels being spared.

It has been recognized that many normal human tissues, such as the renal glomeruli (Gelfand *et al.*, 1975) or the choroid plexus (Braathen *et al.*, 1979) contain apparent receptors for components present in immune complexes, thus determining the anatomical site of deposition. In addition, prior tissue damage within an organ may also predispose certain sites to injury by circulating immune complexes.

The ultrastructural examination of the sural nerve of patients with vasculitis and immunoglobulin deposition revealed abnormalities of the endoneurial vessels, such as swollen and hypertrophied endothelial cells with numerous and irregular intraluminal cytoplasmic projections. The endothelial changes may be explained by inflammatory involvement of the intima of capillaries and small endoneurial vessels. On the other hand, it has recently been recognized that the endothelial structures have an active role in different immunological events (Pals *et al.*, 1986), although a direct relationship between the antigenicity of human vascular endothelia and the pathogenesis of vasculitis has not previously been observed (Piomelli *et al.*, 1959).

Similar ultrastructural alterations in endoneurial vessels were found in 5 other patients. They showed exposure of basal lamina to the lumen resulting from discontinuity between endothelial cells. This could result from the release of vasoactive amines that usually occurs in immune complex diseases. The complexes induce the release from the platelets of vasoactive mediators which cause separation of endothelial cells. The resulting increase in vascular permeability leads to deposition of large complexes on exposed basal laminae with an ensuing inflammatory reaction.

In most of our patients we found histological evidence of vascular abnormalities, ranging from moderate vessel wall changes to acute vasculitis of small-sized arteries with perivascular lymphocyte-monocyte infiltration. These alterations may influence the microcirculation of nerve and produce ischaemic damage. The morphological data evidenced axonal degeneration and selective vulnerability of large myelinated fibres, without signs of primary myelin involvement. No immunoglobulin reacting with myelin or axons or cryoglobulin aggregates occluding the lumen of capillaries were found. We think that these two mechanisms of nerve damage might be observed in type I cryoglobulinaemia, but in types II and III cryoglobulinaemia the neuropathy is mainly due to ischaemia resulting from inflammatory vascular destruction caused by a hypersensitivity reaction.

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# PROCESSING OF SEMANTIC ANOMALY BY RIGHT AND LEFT HEMISPHERES OF COMMISSUROTOMY PATIENTS

## EVIDENCE FROM EVENT-RELATED BRAIN POTENTIALS

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## SUMMARY

The ability of 5 commissurotomized patients to appreciate semantic anomalies presented to their right and left hemispheres was tested using both electrophysiological and behavioural measures. In all cases, the patients heard sentence fragments that were completed either by semantically congruous or incongruous words briefly flashed to the left visual field, right visual field or to both fields simultaneously. A dissociation between behavioural and event-related brain potential (ERP) measures was observed. All 5 patients were able to indicate by a pointing response with greater than chance accuracy whether the terminal word of a sentence made sense (i.e., appropriate for the context) or was nonsensical. This was true regardless of the hemisphere receiving the terminal word. Likewise, all the patients responded to right visual field anomalies with a cerebral potential (N400) that was typically elicited by such words in control subjects. In contrast, only those 2 patients who developed an overt speech capability under the control of the right hemisphere produced N400 waves in response to left visual field anomalies. These findings were interpreted as suggesting possible relationships within language generation and semantic priming.

## INTRODUCTION

In recent years there have been extensive neuropsychological and electrophysiological investigations of the brain processes subserving language comprehension and production (*see* Kertesz, 1979; Ojemann, 1983; Patterson *et al.*, 1985; Kutas and Van Petten, 1988). Many of these studies have been aimed at further delineating the respective contributions of the two cerebral hemispheres in speech and linguistic analyses. At the core of the neuropsychological approach has been the assessment of linguistic abilities and deficiencies of each of the cerebral hemispheres in persons with abnormal brain organization. Among the various types of patients that have been studied are those with discrete lesions in one of

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the hemispheres, an entire hemisphere removed surgically, unilateral hemisphere anaesthesia with sodium amylobarbital, and surgical or congenital disconnection of the left and right cerebral hemispheres.

The neuropsychological evidence demonstrates that most language functions are asymmetrically distributed, with the left cerebral hemisphere bearing the greater share of the processing load. Assuming no early brain damage, the left hemisphere of most individuals appears to subserve both speech and language comprehension in written, oral and gestural form. The contribution of the right hemisphere during normal language processing, for other than the prosodic and pragmatic aspects of language processing, is controversial. The positions taken range from those in which the right hemisphere plays little or no role in normal language processing (Rasmussen and Milner, 1977; Gazzaniga, 1983), to those that suggest its contribution to semantic analysis may parallel that of the left hemisphere (*see* Zaidel, 1981, 1985; Lambert, 1982*a*, *b*, 1983; Patterson and Besner, 1984; Curtiss, 1985). Whatever the case may be, studies of right hemisphere language functions have reinforced the idea that 'language' is not a unitary phenomenon and that it is necessary to define the respective roles of the cerebral hemispheres in mediating different aspects of language (e.g., Coltheart *et al.*, 1980).

The lateralization of language processes has been investigated using a variety of techniques. In particular, experiments with split-brain individuals have allowed detailed comparisons of the language functions in the surgically separated hemispheres (*see* Gazzaniga, 1970; Sperry, 1974; Gazzaniga and LeDoux, 1978; Benson and Zaidel, 1985). In the national population of split-brain patients in the USA who have been extensively examined for right hemisphere language, 5 are of particular interest (Gazzaniga, 1983). While there is good evidence that the right hemispheres of all 5 of these patients can comprehend spoken and written language with some facility, it has proved difficult to establish the extent to which the operating principles of comprehension in the right hemispheres of the different cases are similar to one another or to those of their left hemispheres. A particularly vexing problem has been to compare semantic processing in the right hemispheres of the different patients when only the left was capable of verbal report. While some ingenious experimental techniques for tapping into the mute right hemispheres have been developed, indices of comprehension based on pointing and matching behaviours may not always reveal qualitative differences in the underlying operations.

Another approach towards assessing right hemisphere language is to supplement behavioural observations with electrophysiological recordings of the synchronized brain activity elicited across the scalp by words in a written or spoken message (for review, *see* Rugg *et al.*, 1986). These responses, known as event-related brain potentials (ERPs) are useful in that they allow on-line monitoring of brain activity during linguistic processing, whether or not the person responds overtly to the stimulus material. Of the available ERP measures, we chose a component that is elicited reliably during the processing of semantically incongruous or unexpected words in a sentence context; this negative wave, termed N400, is triggered by words that deviate from an established semantic context and shows a maximum amplitude at around 400 ms after word onset (e.g., Kutas and Hillyard, 1984; Neville *et al.*, 1986). For example, a nonsensical word at the end of a sentence ('Every Saturday morning he mows the *chair*') elicits an N400 that is not seen in the ERP elicited by a more predictable word such as 'lawn' at the end of this same sentence. The N400 appears to be a general response to semantic incongruity, regardless of the input modality, since it can be elicited by spoken and printed words as well as the signs of American Sign Language (Neville, 1985; Kutas *et al.*, 1987). In so far as it has been tested, the N400 seems to be elicited specifically by semantic rather than grammatical or physical incongruities within prose (Kutas and Hillyard, 1980*b*, 1983; McCallum *et al.*, 1984).

Whereas the largest N400s are elicited by semantic anomalies, words that are not anomalous also elicit N400s with an amplitude that corresponds to their unexpectedness or unpredictability within a given context (e.g., Fischler *et al.*, 1983, 1984; Harbin *et al.*, 1984; Kutas and Hillyard, 1984; Kutas *et al.*, 1984). Thus while some uncertainty exists as to the exact nature of the semantic analyses indexed by the N400, such findings have led to the proposition that N400 amplitude is an inverse function of the amount of semantic priming (or degree of semantic constraint) that a word has received from a preceding context (Kutas and Hillyard, 1984; Bentin *et al.*, 1985). According to this view, this ERP marker may well be tracking one of the more automatic language processes that are presumed to occur during semantic processing. Whether or not this conception of the N400 proves to be wholly correct, it is clear that the elicitation of large N400s by anomalous or unpredictable words reflects a fairly high level of semantic processing, namely, an ability to appreciate the semantic relationship between a word and the verbal context within which it occurs.

By examining the N400 wave in split-brain patients who differ in their right hemisphere language capacities, we hope to elucidate further the language function(s) that must be present in order for this ERP response to occur and thereby learn more about the nature of the processing events that underly the N400. Moreover, by presenting words separately to the left and right hemispheres and by recording the ERPs indicative of the semantic analyses initiated in each hemisphere, we can evaluate whether the separated right hemispheres of split-brain patients carry out the semantic analyses reflected in the N400 in the same manner as do their left hemispheres. An affirmative answer would argue for a qualitative similarity between the semantic systems of the right and left cerebral hemispheres.

## METHODS

### *Control subjects*

Nine normal young adults (5 male, age range 18–32 yrs) were paid for participating in this experiment. All of the subjects were right-handed according to self-report and the Edinburgh

Inventory (Oldfield, 1971). Only 1 of these subjects had a member of their immediate family who was left-handed.

*Commissurotomized patients*

The case histories of the 5 split-brain patients are summarized below (for further details, *see* Gazzaniga *et al.*, 1984*a*).

*Case 1.* P.S. is a right-handed male, 20 yrs of age at the time of testing (Wilson *et al.*, 1977). He experienced a series of right-sided motor seizures at 20 months of age. He was without seizures until aged 4 yrs, when he experienced 'absences' about twice a month. At the age of 10, he began to have right-sided partial seizures and was found to have an abnormal EEG over the left hemisphere; seizures recurred over the next 5 yrs and proved intractable. At aged 15, he underwent complete surgical section of the corpus callosum. Since his operation, he has remained largely free of seizures. Magnetic resonance imaging (MRI) showed the callosum to be fully sectioned with no evidence of other brain damage.

*Case 2* V.P. is a right-handed female (27-yrs-old when tested) who had experienced recurrent seizures starting at 9 yrs of age (Sidtis *et al.*, 1981). Anticonvulsant drugs controlled the seizures until the age of 27 yrs, when she began experiencing grand mal, petit mal and myoclonic episodes while on multiple anticonvulsants. That year she underwent partial anterior callosal section at the Medical College of Ohio; the resection of her corpus callosum was completed in a second operation 7 wks later. She was tested 6 months after this second operation. MRI has since revealed sparing of a few fibres both in the rostrum and splenium (Gazzaniga *et al.*, 1984).

*Case 3.* J.W. is an alert right-handed male (26-yrs-old when tested) with a history of staring spells, reportedly since the age of 13 yrs (Sidtis *et al.*, 1981). After his first major motor seizure at 19 yrs of age, frequency of the seizures increased and they became intractable (Wilson *et al.*, 1982). Midline section of the corpus callosum was performed in two stages by Dr Donald Wilson of the Dartmouth Medical School at the age of 25 yrs. The posterior half of the corpus callosum, including the splenium, was sectioned first, with the remaining anterior portion sectioned in a second operation 10 wks later. MRI has verified complete callosal sectioning.

*Case 4.* N.G. is a right-handed woman who was tested at the age of 47 yrs. She had a left temporal EEG focus and evidence for a right central lesion in the form of rolandic calcification 1 cm wide, as well as left-sided numbness preceding some of her preoperative convulsions. As a result of intractable epilepsy that began when the patient was 18 yrs of age, a single stage complete cerebral commissurotomy (including the anterior commissure, corpus callosum, massa intermedia and right fornix) was performed at 30 yrs of age. The operation was performed by Drs P. J. Vogel and J. Bogen at the White Memorial Medical Center in Los Angeles (Bogen *et al.*, 1965).

*Case 5.* L.B., a right-handed male, 28-yrs-old at testing, had demonstrated generalized EEG abnormalities. His epilepsy began at 3½ yrs of age. Surgery was performed by Dr Vogel and his colleagues at age 13 yrs. The approach for the complete single-stage commissurotomy was, as with Case 4, by retraction of the right hemisphere.

*Procedure*

All experiments were conducted with the informed consent of the subjects and patients.

During all runs, subjects sat in a reclining chair in an unshielded experimental room. At the start of each trial block they were asked to fixate a dot in the centre of either (1) a translucent screen on which visual stimuli (terminal words of sentences) were back-projected from a slide projector, or (2) a video monitor on which the words were flashed under the control of a microcomputer.

Each of the split-brain subjects and the 9 control subjects were presented with 319 seven-word sentences in 16 blocks of 20 each, following a block of 20 practice trials. A warning tone preceded each sentence by approximately 1 s. The first 6 words of each sentence were presented auditorily (binaurally), through headphones, at interword intervals of about 600 ms. Each sentence was completed by a 180 ms duration flash of a pair of words, one in each visual field. The words

TABLE 1. EXAMPLES OF INCOMPLETE SENTENCES AND WORDS PRESENTED FOR COMPLETION TO THE LEFT AND RIGHT VISUAL FIELDS

| | *Visual terminal words* | |
|---|---|---|
| *Auditory phrase* | *LVF* | *RVF* |
| 1. The mechanic decided to join a | union | union |
| 2. She ran the mile in four | candies | minutes |
| 3. The two suspects were arrested for | murder | cereal |
| 4. He towed the car from the | juice | juice |

LVF = left visual field, RVF = right visual field.

averaged 5.16 letters in length and were 1.2° high. The medial aspect of each word was situated 1.5° lateral to the fixation point. Maintenance of fixation was monitored by the horizontal electroculogram (EOG).

For 204 of the sentences, the words in the two visual fields were identical to one another and were congruous with the preceding auditory context. The remaining 115 sentences were completed by word pairs in which the word in the left visual field (LVF, N = 38), right visual field (RVF, N = 39) or both fields (N = 38) was semantically inappropriate to the preceding context. A congruous word of equal length was shown in the opposite field for each of the unilateral incongruous words. Examples of the four sentence types are given in Table 1. The 2 obvious choices for visual completion of these sentences were to present a single word randomly in either the right or the left visual field (i.e., unilaterally) or to present 2 words simultaneously in each field (i.e., bilaterally). For the present experiment, we decided to complete the auditory sentence fragments with bilateral word presentations for several reasons. First, experience has shown that control subjects and patients alike are much less prone to make disruptive horizontal eye movements when they are required to read 2 words, one in each visual field, at the same time (especially for exposure durations of less than 200 ms). Secondly, since each sentence frame was presented auditorily (binaurally) we assumed that each hemisphere was awaiting a visual completion. By providing a completion for both hemispheres, we hoped to reduce the effect of ERP components known to be associated with the surprise at receiving nothing (Renault, 1983) and to increase our control of the stimuli that each hemisphere received. In future work, we also plan to evaluate ERP changes with unilateral visual presentations.

After each block of 20 trials during the ERP recording session, the subject was asked to recall by verbal report the terminal words of several of the sentences they had just received. Control subjects were tested for recall on all of the sentences. In this delayed recall task, the experimenter read the first 6 words of the sentence, and the patient was asked to report the word or words they remembered as having completed that sentence. Since the commissurotomized patients had a tendency to report a congruent ending regardless of the word actually presented, they were given occasional reminders that some of the sentences were terminated by nonsensical words. In addition, for a few of the sentences chosen at random, the patients' word recognition was probed by asking them to write the word they had seen (presumably the one presented in the left visual field), on a piece of paper with their left hand. These tasks served to keep the subject attentive to the stimuli and provided further information about how well the visually presented words were being perceived.

In addition, in separate sessions without ERP recordings, the split-brain subjects were presented a series of unilateral words flashed for 180 ms to the left or right visual fields at random. Their task was to name the word seen as quickly as possible. Common words, 3-5 letters in length, were flashed with the medial aspect located 1.5° from the fixation point. This task was aimed at testing for the possibility of expressive speech under the control of the right hemisphere (as would be evidenced by the ability to name left-field words).

Also in a separate session, the ability of the split-brain subjects to appreciate semantic anomalies with the right and left cerebral hemispheres separately was tested. The subjects were presented with a series of sentences one at a time. All but the final word of each sentence was presented auditorily. The final word was flashed unilaterally for a duration of 180 ms randomly either to the right or the left visual field. The subjects' task was to point to the word SENSE or NONSENSE written on a card in their lap, depending upon whether or not the flashed word made sense as a completion to the preceding sentence fragment. Half the sentences were semantically congruous and half were semantically anomalous. Of the anomalous sentences, half were completed by a word semantically related to the expected completion for that sentence whereas the other half were completed by a word that was semantically unrelated to any word in the sentence.

Our primary aim with this behavioural test was to find out whether each hemisphere could determine, in isolation, whether sentences did or did not make sense. Experience with bilateral stimulation (a sensible word in one field and a nonsensical one in the other) indicated that the patients found making an overt judgement (e.g., pointing or verbal report) under such conflicting conditions to be difficult and disturbing. The emotionality observed under bilateral conditions was not observed during the ERP recordings when the subjects' task was only to read for comprehension and subsequent recognition or recall. Also, with a pointing response under bilateral conditions, it was impossible to determine which hemisphere was controlling the response. Since neither horizontal eye movements after 180 ms nor the surprise of the unstimulated hemisphere posed any problem for interpretation of these behavioural results, we decided to probe the comprehension of each hemisphere's ability by completing the auditory sentence fragments with random unilateral visual presentation.

### *Recording system*

For the patients, the EEG was recorded from 6 electrodes, each referred to linked mastoid electrodes, placed according to the International 10–20 convention (Jasper, 1958) at central (C3, Cz, C4) and parietal (P3, Pz, P4) midline and lateral locations. For the control subjects, the EEG was recorded from 14 electrodes, each referred to the left mastoid, placed at frontal (Fz, F7, F8), central (Cz, C3, C4), temporal (T5, T6), parietal (Pz, P3, P4), occipital (O1, O2) and the right mastoid (A2) locations. Nonpolarizable Ag-AgCl electrodes were secured to the subject's scalp with collodion. Electrode impedances did not exceed 2 kΩ. Eye movements and blinks were monitored via an electrode placed on the lower orbital ridge, referred to linked mastoid electrodes in the patients and to the left mastoid electrode in the controls. In addition, a bipolar right external canthus to left external canthus montage (horizontal EOG) was used to record lateral eye movements. Midline and horizontal EOG channels were recorded with d.c. preamplifiers (high frequency cut-off 40 Hz), and lateral channels with an 8 s time constant (high frequency cut-off 100 Hz).

## RESULTS

### *Control subjects*

### *Behavioural performance*

The control subjects' performance data (mean percentage correct and SD) on the delayed recall of sentence completions are presented in Table 2. In general, terminal words were better recalled if they were congruous than if they were incongruous. In addition, more endings (whether congruous or incongruous) were recalled (by about 15%) if the same word had been presented in each visual field than if 2 different words were shown. There was no interaction between visual field and congruity in determining recall accuracy.

TABLE 2. CONTROL SUBJECTS: PERCENTAGE CORRECT FOR CUED RECALL OF SENTENCE TERMINAL WORDS PRESENTED TO LEFT (LVF) AND RIGHT VISUAL FIELD (RVF). MEANS (±SD)

| Terminal word pair RVF/LVF | *LVF* | *RVF* |
|---|---|---|
| Cong./Cong. | 93.5 (0.1) | 93.5 (0.1) |
| Cong./Anom. | 77.4 (13.7) | 37.4 (25.0) |
| Anom./Cong. | 34.7 (21.8) | 74.0 (15.2) |
| Anom./Anom. | 52.2 (18.0) | 52.2 (18.0) |

## *ERP findings*

The grand average ERPs (n = 8) recorded from the central electrode locations in response to the visually presented terminal words of the sentences are shown in fig. 1. One subject's data were not included because of excessive artifact. In each column, the ERPs elicited by bilaterally congruous endings are compared with the ERPs elicited by unilateral or bilateral incongruous endings, with the incongruity presented either in the right, left or both visual fields, respectively. In all cases the ERP waveform was dominated by a broad positive (downward)

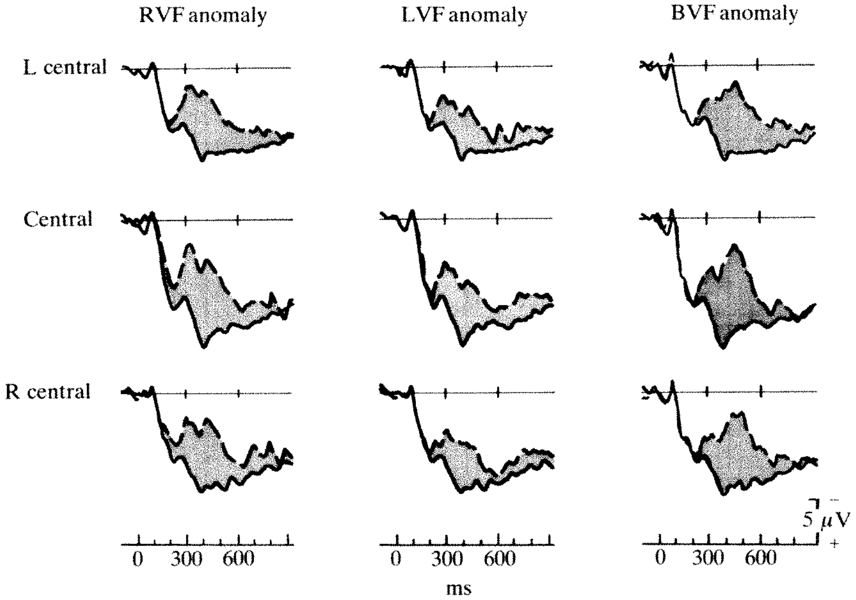

FIG. 1. Grand average ERPs from control subjects (n = 8) elicited by sentence terminal words from midline (central, Cz), left central (C3) and right central (C4) scalp locations. In each column the response to bilateral congruous endings (solid tracings) is compared with the response to the indicated type of anomalous ending. The anomalous endings also consisted of a bilateral word pair with the word in either one (LVF or RVF) or both (BVF) visual fields being semantically anomalous relative to the preceding sentence context. In this and all subsequent figures negativity is plotted upwards. Continuous line = congruous; broken line = semantically anomalous.

deflection that represents, in part, the termination of the sustained negativity (Contingent Negative Variation) that develops during sequential word presentations (e.g., Kutas and Hillyard, 1980*a*, *b*). For congruous endings, this late positivity peaked at around 380 ms at the centroparietal sites where it was the largest.

The late positive complex appeared to be composed of early (300–600 ms) and late (600–900 ms) subcomponents having different scalp distributions. Both the early and the late phases were most positive at the vertex site. For the early phase, the potential at the remaining sites expressed as a percentage of maximum amplitude, was as follows: Fz (65), Pz (92), L frontal (33), R frontal (43), L central (77), R central (85), L temporal (29), R temporal (36), L parietal (61), R parietal (69), L occipital (29) and R occipital (38). The amplitude of the later phase fell off more rapidly towards the back of the head than did the earlier positivity. The late phase potential expressed as a percentage of maximum amplitude was as follows: Fz (71), Pz (70), L frontal (50), R frontal (52), L central (79), R central (80), L temporal (17), R temporal (12), L parietal (47), R parietal (48), L occipital (8) and R occipital (9).

The ERPs elicited by incongruous endings included a broadly distributed negativity between 250 and 600 ms (i.e., the 'N400 effect') superimposed on the late positive deflection. The N400 effect (fig. 1, shaded area) began at a latency of around 200 ms, peaked between 400 and 450 ms and lasted for 300 to 400 ms. The amplitude of the N400 effect was quantified from the 'difference waves' formed by subtracting the ERPs to the congruous endings from those to the anomalous endings (Table 3). These data were analysed by repeated measures ANOVA, with factors of visual field of anomaly (left, right, both) and electrode site (13 levels). These analyses employed the Greenhouse-Geisser correction for inhomogeneity of covariance (Keselman and Rogan, 1980).

On the whole, the amplitude, latency and scalp distribution of the N400 effect in the control subjects was similar whether the anomalous word was presented to the right or left visual field (*see* Table 3). The slight tendency for the N400 to be larger in response to anomalies in the right visual field was not statistically significant. Likewise, while there was a slight tendency for the difference wave to begin earlier (between 100–200 ms) following right than left visual field anomalies at the frontocentral sites, this was not statistically significant; it is possible that with many more trials this difference would have proven real. In contrast, the peak amplitude of the N400 difference wave following bilateral anomalies was significantly larger than that following either of the single visual field anomalies (peak amplitude between 300–600 ms relative to 100 ms prestimulus baseline, $F(2, 14) = 5.37$, $P < 0.024$, epsilon $= 0.61$; mean amplitude 300–600 ms, $F(2, 14) = 5.43$, $P < 0.048$, epsilon $= 0.76$). There was also a slight tendency for the N400 difference wave in association with bilateral anomalies to peak somewhat later (427 ms at Cz) and to be more prolonged than that to either right visual field (403 ms) or left visual field (391 ms) anomalies.

TABLE 3 CONTROL SUBJECTS PEAK AMPLITUDE OF N400 DIFFERENCE WAVE* IN μV (SE) OVER THE RANGE 300–600 ms POSTSTIMULUS

| | *Anomalous word in.* | | |
|---|---|---|---|
| *Electrode site* | *RVF* | *LVF* | *Both VF* |
| Frontal | −9.57 (1.13) | −7.33 (0.60) | −8.95 (0.97) |
| Central | −10.90 (1.58) | −8.28 (0.55) | −11.75 (1.13) |
| Parietal | −9.12 (1.35) | −7.82 (0.85) | −11.10 (1.28) |
| L frontal | −5.51 (0.73) | −4.45 (0.29) | −5 15 (0.77) |
| R frontal | −6.81 (1.12) | −5.80 (1.04) | −6.57 (1.03) |
| L central | −9.19 (1.21) | −7.39 (0.66) | −10.55 (1.09) |
| R central | −9.67 (1.22) | −7.73 (0.89) | −10.79 (1.15) |
| L temporal | −4.85 (0.80) | −4.05 (0.74) | −6.82 (0.94) |
| R temporal | −6.42 (0.67) | −5.27 (0.74) | −7.44 (1.19) |
| L parietal | −7.91 (1.00) | −7.03 (1.16) | −9.54 (1.22) |
| R parietal | −8.37 (0.84) | −7.23 (1.06) | −9.62 (1.16) |
| L occipital | −5.81 (0.44) | −5.11 (0.96) | −7.52 (0.92) |
| R occipital | −6.09 (0.73) | −6.02 (1.05) | −7.40 (1.07) |

* Difference waves calculated by subtracting the ERPs to the bilateral congruous endings from those to the indicated type of anomalous ending. Peak amplitude is relative to 100 ms prestimulus baseline

## *Split-brain subjects*

### *ERP findings*

Substantial N400 waves were elicited in all the split-brain patients by word pairs when the right visual field contained an anomalous word (*see* figs 2, 3). Thus when the language dominant hemisphere saw the anomaly, an N400 of near normal amplitude but of somewhat prolonged latency was elicited (Table 4). In contrast, the patients varied considerably in the amplitude of the N400 elicited by left visual field anomalies. To illustrate these differences, the ERPs were averaged separately for the 2 subjects (Cases 1, 2) who showed sizeable N400s to left field anomalies (fig. 2) and for the 3 subjects (Cases 3–5) who showed much smaller N400s for anomalies flashed to the right hemisphere (fig. 3). The N400 difference waves for Cases 1 and 2 (fig. 4, middle traces) show the N400 effect to be of relatively similar amplitude for left and right visual field anomalies and slightly larger over the right than the left hemisphere at the central and parietal scalp sites; this lateral asymmetry did not differ according to the visual field in which the triggering anomalous word was presented. For the other 3 patients (fig. 4, lower traces), the N400 was also slightly larger over the right hemisphere for right field anomalies, whereas its amplitude was near noise levels for left field anomalies.

Although statistical analyses of data from so few subjects are lacking in power, the difference between the two groups of patients was verified by testing whether the N400 (area measure 300–600 ms at the P4 electrode site) elicited by the right and by the left field anomalies was significantly greater than zero. This was true

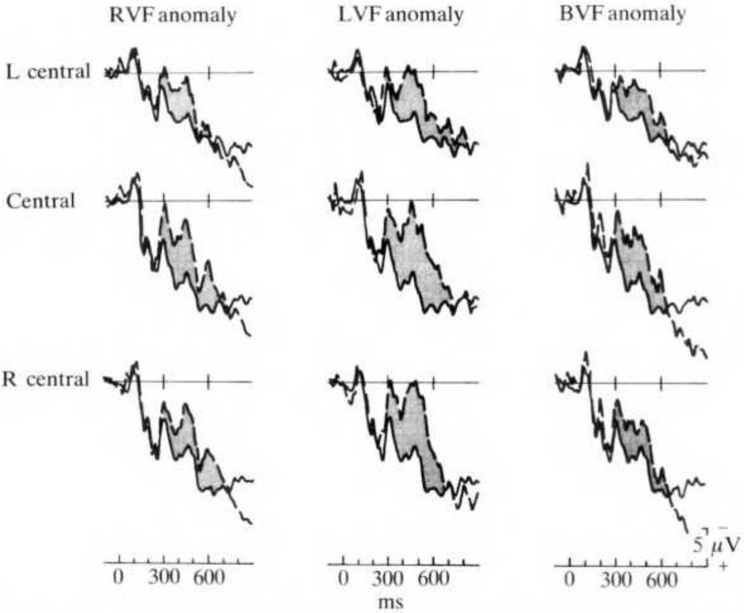

FIG. 2. Comparison of ERPs recorded at central scalp locations following semantically congruous and anomalous sentence endings. ERPs are averaged across commissurotomized *Cases 1 and 2* (P.S. and V.P.), who showed a similarly enlarged late negativity (shaded areas) to semantic anomalies presented to the left visual field. Continuous line = congruous; broken line = semantically anomalous.

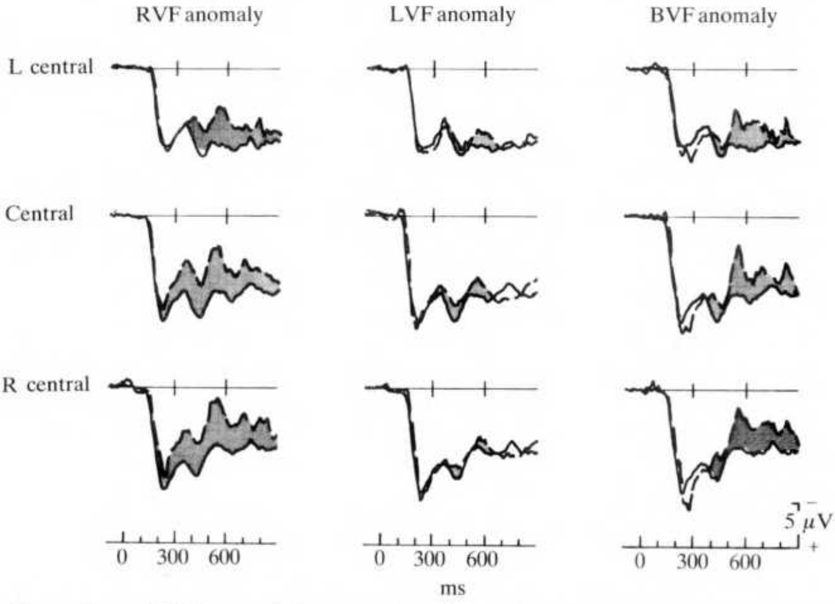

FIG. 3. Comparison of ERPs recorded at central scalp locations following semantically congruous and anomalous sentence endings. ERPs are averaged across commissurotomized *Cases 3–5* (J.W., L.B. and N.G.), who showed a similarly reduced late negativity (shaded areas) to semantically anomalous endings presented in the left visual field. This pattern was distinct from that shown by *Cases 1 and 2* (P.S. and V.P.). Continuous line = congruous; broken line = semantically anomalous.

TABLE 4. MEAN AMPLITUDE* OF N400 DIFFERENCE WAVE AT DIFFERENT ELECTRODE SITES FOR SEMANTIC ANOMALIES IN RIGHT, LEFT AND BOTH VISUAL FIELDS

| | *Semantic anomaly in* | | |
|---|---|---|---|
| | *RVF* | *LVF* | *Both VF* |
| Control Ss (n = 8) | | | |
| Cz | −6.05 (1.25) | −4.11 (0.37) | −6.94 (1.02) |
| Pz | −4.40 (1.53) | −3.43 (0.57) | −6.64 (1.16) |
| C3 | −5.11 (0.69) | −3.66 (0.49) | −5.88 (0.64) |
| C4 | −5.35 (1.11) | −3.62 (0.71) | −6.33 (0.98) |
| P3 | −3.71 (0.93) | −2.98 (0.95) | −5.51 (0.78) |
| P4 | −3.80 (1.08) | −2.87 (0.46) | −5.78 (1.02) |
| Commissurotomized patients (Cases 1, 2) | | | |
| Cz | −5.27 (0.69) | −7.24 (2.23) | −4.97 (1.96) |
| Pz | −4.66 (1.61) | −4.27 (1.20) | −4.70 (1.86) |
| C3 | −2.88 (1.70) | −4.50 (2.97) | −3.27 (2.02) |
| C4 | −3.90 (1.80) | −7.24 (2.39) | −3.51 (1.62) |
| P3 | −3.92 (0.87) | −4.13 (0.98) | −2.97 (1.70) |
| P4 | −5.62 (1.12) | −5.04 (1.05) | −4.06 (3.21) |
| Commissurotomized patients (Cases 3–5) | | | |
| Cz | −4.17 (0.36) | −1.45 (0.89) | −1.82 (2.08) |
| Pz | −4.73 (1.11) | −1.20 (1.00) | −2.86 (1.71) |
| C3 | −2.24 (0.56) | −0.81 (0.70) | −1.14 (0.66) |
| C4 | −4.03 (1.11) | −0.52 (1.15) | −1.66 (2.29) |
| P3 | −2.62 (0.59) | −1.31 (0.96) | −1.97 (0.84) |
| P4 | −4.11 (0.39) | −0.75 (1.06) | −2.19 (1.30) |

* N400 amplitude measured as mean voltage in $\mu$V (SE) in difference waves over the interval 300–600 ms poststimulus relative to 100 ms prestimulus baseline.

for Cases 1 and 2 for both right ($t(1) = 27.0$, $P < 0.02$) and left ($t(1) = 45.8$, $P < 0.01$) field anomalies; for Cases 3–5, however, the N400 was significant for right ($t(2) = 10.56$, $P < 0.01$) but not for left ($t(2) = 0.71$, n.s.) field anomalies. Calculated a different way, the parietal N400 amplitude for Cases 1 and 2 did not differ significantly between right and left field presentations (−5.62 versus −5.04 $\mu$V), whereas for Cases 3–5 this difference (−4.12 versus −0.75 $\mu$V) was significant ($t(2) = 4.79$, $P < 0.05$). The N400 difference waves for left and right field anomalies are shown individually for each of the subjects in fig. 5.

As previously noted, for the control subjects the bilateral anomalies elicited N400 amplitudes that were larger and somewhat later than either single field anomalies. Among the patients, Cases 2 and 5 showed a pattern similar to the controls. The remaining patients generated either a very small N400 apparently overlapped by a large late positivity (Case 1), a very late response between 500 and 900 ms (Case 3) or none at all (Case 4) in response to bilateral anomalies. Because of the lack of N400 in Case 4, the ERP averaged over the second group of split-brain subjects (fig. 3) shows the bilateral anomalies to elicit smaller N400 amplitudes than the right field anomalies. In no group did the amplitude of the N400 to bilateral anomalies approach the sum of the 2 unilateral responses; such a result would have suggested that the stimuli in the 2 fields activated wholly independent cerebral systems.

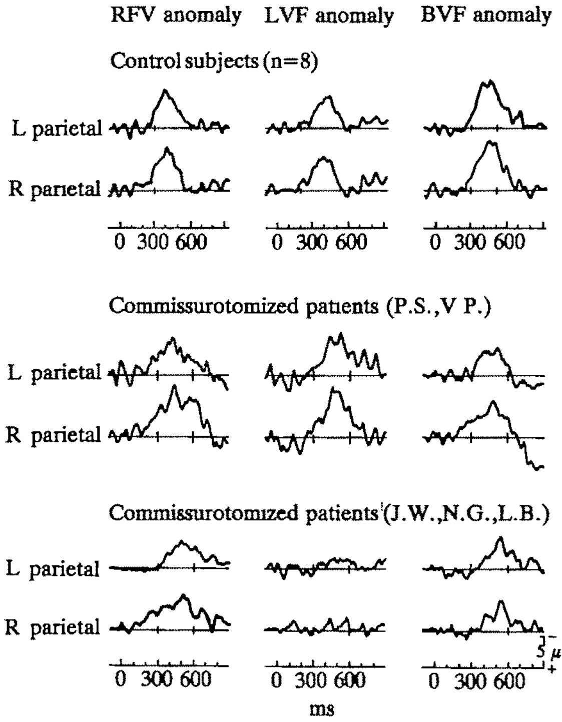

FIG. 4. Grand average difference waveforms for control subjects, for *Cases 1 and 2* (P S. and V.P.), and for *Cases 3-5* (J.W., N.G. and L.B.). In each case the difference wave represents a point-by-point subtraction of the ERP elicited by bilaterally congruous endings from the ERP to the indicated type of anomalous ending.

### *Behavioural observations*

In the tests where unilateral words were flashed and immediate verbal responses were given, all split-brain subjects accurately reported more than 75% of the words that were flashed in the right visual field. The errors made were reports of visually similar words or word fragments, as would be expected with brief visual presentations. Case 1 was unique, however, in also being able to name immediately the word flashed to the left visual field on over 80% of the trials. This is consistent with previously reported observations on this subject during this period (Gazzaniga *et al.*, 1979). Case 5 reported verbally the left field word correctly about half the time (7/16 trials), but he only did so after a response delay of 10-15 s, suggestive of a cross-cueing strategy (*see* Discussion). Cases 2, 3 and 4 were unable to name the words flashed to the left visual field.

During the ERP recording runs when subjects were questioned about a few of the terminal words they had seen after each block of 20 sentences, there was a

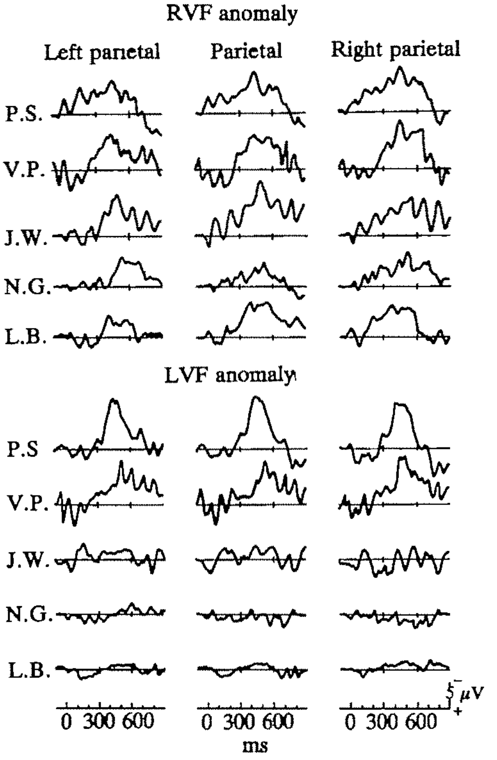

FIG. 5. Difference waves (anomalous minus congruous) for each of the commissurotomized patients obtained from recordings taken over midline (Pz), left parietal (P3) and right parietal (P4) scalp. The upper and lower halves of the figure show responses to semantically anomalous endings presented in the right and left visual field, respectively

strong tendency to report the most probable and expected terminal word for a given sentence frame, even when an anomalous word had actually been presented. For example, when the sentence frame 'We want to buy a new microwave . . .' was read to the subjects in the delayed recall task, the majority responded they had seen 'oven', even though 'road' had actually been presented in both visual fields. This illustrates the difficulty the patients had in remembering the anomalous endings over a number of intervening sentences together with the strength of context in provoking a congruous response. Thus the subjects reported the congruous words presented to the right visual field with a mean accuracy of 88% correct (range 78–96%), whereas only 22% (range 13–32%) of the incongruous words shown to the right field were reported correctly. Erroneous congruous responses were given on 61% of the trials with right field anomalies, and failures to respond occurred on 16%. The fact that subjects were as accurate as 13 to 32% in this difficult memory test, however, does indicate that they were generally attentive to the stimuli.

Except for Case 1, there was not a single instance in this recall test of a subject reporting verbally an incongruous word that had been delivered only to the left visual field (i.e., when the right field word was congruous). This indicates that the delayed verbal report was completely under the control of the left hemisphere in

Cases 2–5. Case 1 verbally reported incongruous endings correctly 13% of the time for right field presentations and 22% of the time for left field presentations, indicating participation of both hemispheres.

TABLE 5 PERCENTAGE CORRECT OF SENSE/NONSENSE JUDGEMENTS FOR AUDITORY SENTENCES COMPLETED BY UNILATERALLY PRESENTED WORDS

| Case | *1* | *2* | *3* | *4* | *5* |
|---|---|---|---|---|---|
| LVF | 91 | 80 | 76 | 70 | 75 |
|  | (125) | (127) | (129) | (43) | (32) |
| RVF | 75 | 92 | 90 | 87 | 95 |
|  | (131) | (127) | (126) | (45) | (39) |

Numbers of trials in parentheses.

All the commissurotomized patients were above chance at indicating by a pointing response whether a word presented to the right or left visual field completed a spoken sentence fragment sensibly or nonsensically. All the patients were significantly ($F(1, 4) = 10.58$, $P < 0.03$) more accurate in judging sense than nonsense (LVF: congruous endings 83% correct, anomalous endings 73%; RVF: congruous 95%, anomalous 79%). Across all subjects judgement accuracy was only slightly worse for semantically related than unrelated anomalies (LVF: related 70%, unrelated 76%; RVF: related 79%, unrelated 80%). With the exception of Case 1, all the patients showed a right visual field advantage (*see* Table 5).

## DISCUSSION

The ERP results from this experiment are in line with the view that the language systems of the right cerebral hemisphere are quite variable among split-brain patients (Gazzaniga, 1983). Only 2 of the 5 patients (Cases 1, 2) demonstrated N400 amplitudes in the normal range in response to semantically anomalous words presented to the right hemisphere; in fact, at some electrode sites these N400s were slightly larger than those following anomalous words presented to the patients' left hemispheres. In contrast, all patients showed sizeable N400 waves when the left hemisphere encountered an anomalous sentence ending. Taking the N400 as an index of a language processing capability that is reliably present in the vast majority of normal individuals (Kutas and Hillyard, 1980*a*, 1983), it would appear that this capability is less fully developed in the right hemispheres of Cases 3–5 than in the right hemispheres of Cases 1 and 2 or in the left hemispheres of either patients or controls.

If we assume that similar electrophysiological configurations imply a qualitative similarity of underlying processing mechanisms, it would follow that the right hemispheres of Cases 1 and 2 possess a language analysis system that is similar in kind to that employed by their left hemispheres (and also by normal brains).

Indeed, in these 2 patients the N400 waves were highly similar in morphology (monophasic negativity), amplitude and scalp distribution for right and left visual field anomalies. The extent to which this similarity of their left and right hemisphere processing systems extends to aspects of language other than the subset that is manifested in the N400 is unclear, but it does not appear to hold for all aspects of syntactic processing. Although Cases 1 and 2 have demonstrated more syntactic competence with their right hemispheres than Cases 3-5, the left hemisphere of Case 1 is appreciably more sophisticated in dealing with syntactic constructs than is her right hemisphere (Baynes and Gazzaniga, 1988). It is also unclear whether the lack of N400 in response to right hemisphere anomalies in Cases 3-5 is due to a reduced capacity (i.e., quantitative in nature) or to a qualitatively different language analysis system that does not engender a robust N400 wave. It should also be noted that the N400 latencies were somewhat longer in the patients than in the normal control subjects. This may be a consequence of the patients anticonvulsant medication and/or processing delays associated with their neurological conditions, which in all cases involved chronic epilepsy.

The ERP data reported here are consistent with behavioural studies showing that Cases 1 and 2 possess more highly developed right hemisphere language than do the other patients. Unlike the other 3 patients, they were able from the time of their operation to respond to written commands and to judge whether or not written words rhymed, and they have shown some degree of syntactic competence for material presented to the right hemisphere (Gazzaniga *et al.*, 1984; *see also* Levy and Trevarthen, 1977). Most dramatically, Case 1 showed evidence for overt speech under the control of the right hemisphere, both in the present test of naming words flashed to the left visual field and in previous studies of a similar nature (Gazzaniga *et al.*, 1979). Although Case 2 was not able to name left visual field stimuli at the time of the present experiments, she did show a relatively high degree of 'generative capacity' with respect to written output (Sidtis *et al.*, 1981). Starting about 6 months after our tests, she began to develop an overt right hemisphere speech capability which was fully developed 2 years later (Gazzaniga *et al.*, 1984). Thus, by several criteria, Cases 1 and 2 both have right hemisphere language systems more akin to those of the normal intact brain than any of the other split-brain patients studied.

There is some early (Butler and Norrsell, 1968; Gazzaniga and Hillyard, 1971; Levy *et al.*, 1972) and more recent (Johnson, 1984*a*, *b*; present study) evidence that Case 5 can name letters, numbers and words presented to the left visual field with better than chance accuracy. It is not clear, however, to what extent this capacity represents speech controlled by the right hemisphere as opposed to an unusual degree of interhemisphere transfer of visual information together with elaborate cross-cueing strategies (Gazzaniga and Hillyard, 1971). In any case, there is no evidence that he has developed the ability to give an immediate and accurate vocal response to words flashed in the left visual field, as do Cases 1 and 2 (Gazzaniga *et al.*, 1984). In our tests of his word naming capabilities, we found

Case 5 to be relatively accurate in naming words flashed briefly to left visual field, but his verbal responses were several orders of magnitude slower than when he named right visual field words. He was consistently and equally slow to name a left visual field word whether or not he was accurate in his report; his naming latencies for a monosyllabic word ranged between 1.5 to 10 s. In addition, unlike his immediate verbal reports of right visual field words, he tended to report left visual field words as a series of individual letters which culminated in the naming of a word. There is even less evidence that Case 4 has the capacity for right hemisphere expressive language (Johnson, 1984*b*), and virtually none for Case 3. Thus there appears to be a general correlation between the generative capacity of the right hemisphere for speech together with at least a moderate level of syntactic competence and its production of an N400 wave to semantic anomalies.

Since our sample size is limited to 5 commissurotomized patients with different medical and experiential histories, it is possible that this correlation between syntactic/generative competence and N400 elicitation is coincidental. However, if we assume that this observed relationship has general validity, some interesting implications may be drawn concerning the organization of language in the brain, in particular about possible relationships between processes of semantic priming and those of comprehension and expression. The first step in this line of reasoning is to document the N400 wave as a reliable index of semantic priming in language and possibly of more general priming processes as well. (Note that we do not use the term priming necessarily to imply an automatic or unconscious mechanism.) Evidence for this relationship comes from several sources. First, studies of ERPs to semantic anomalies at the ends of sentences have shown that N400 amplitude is reduced if the anomaly bears some semantic relationship to the expected completion of the sentence (Kutas *et al.*, 1984). For example, the amplitude of the N400 elicited by a semantically anomalous completion of the sentence fragment ('The pizza was too hot to . . .') was smaller if the anomaly (e.g., 'drink') was associated in meaning with the expected completion ('eat') than if it was not ('cry'). Similarly, Fischler *et al.* (1983) showed that false statements with a high degree of semantic association between the major words of the sentence did not elicit large N400s (e.g., 'A robin is not a bird'), whereas true statements with little semantic association between the major lexical items did (e.g., 'A robin is not a truck'). Further work confirmed that semantic anomaly is not a necessary condition for N400 elicitation; semantically congruent but relatively unexpected or unpredictable words within a sentence context also elicit N400 waves having an amplitude that varies inversely with semantic expectancy, operationally defined in terms of 'cloze' probability (Kutas and Hillyard, 1984). The results of such experiments have led to the proposition that the amplitude of the N400 wave under such conditions provides an index of the degree of association between words, in particular of the extent to which the eliciting item has been primed or constrained by the preceding context (Kutas and Hillyard, 1984). This idea has received additional support from findings that N400 amplitudes to words preceded by semantically related words are reduced relative to when those words are preceded by semantically unrelated items in semantic categorization and lexical decision tasks (Boddy and Weinberg, 1981; Harbin *et al.*, 1984; Bentin *et al.*, 1985; Kutas, 1985; Rugg, 1985; Boddy, 1986).

In studies to date, manipulations of semantic priming have produced the greatest alterations of N400 amplitude. However, it is important to note that semantically anomalous words in sentences generally fail to match a person's expectancies along other linguistic dimensions as well. The appearance of a semantic anomaly may violate orthographic, phonological and grammatical expectancies, and these factors might also make some contribution to overall N400 amplitude. There are indeed reports that N400-like waves are sensitive to phonological (rhyme/nonrhyme) and other forms of expectancy (Stuss *et al.*, 1983; Rugg, 1984; Kramer and Donchin, 1987). Nonetheless, available evidence is consistent with the proposition that semantic anomalies at the ends of sentences elicit large N400s by virtue of their being unprimed, primarily in the semantic realm.

According to this view, a failure to produce an N400 in response to a semantically anomalous word would imply an abnormality of semantic priming mechanisms. Thus the finding that the right hemispheres of Cases 3–5 did not generate an N400 wave following a semantically anomalous word presented to the left visual field suggests a differential organization or utilization of semantic priming operations in their two hemispheres. However, since their right hemispheres were shown to be capable of judging whether or not a word was semantically anomalous when tested behaviourally, there appears to be a dissociation between comprehension and semantic priming mechanisms.

This dissociation holds whether the apparent comprehension of sense/nonsense by the right hemisphere here reflected a true integration and understanding of sentence meaning or semantic association between key words in the sentences. Since many of the congruous sentences in this experiment included a word that was a semantic associate of the sentence terminal word, the patients could have performed with reasonable accuracy without a full understanding of sentence meaning, for example, by deciding to respond 'sense' whenever a semantic relationship was noted and 'nonsense' otherwise. Such a strategy, however, seems to be insufficient to explain their performance completely. For example, the patients were able to decide that sentences were sensible with greater than chance accuracy even if the sentence did not contain a lexical associate of the congruous terminal word (e.g., 'Fred put the worm on the *hook*'; 'Most cats can see very well at *night*'). Moreover, all the patients were more accurate in judging sensible than nonsensical sentences. Had the patients based their judgements solely on the presence or absence of semantic association, they would have been more accurate on the semantically unrelated anomalous than the congruous sentences; this was not the case. Finally, with the exception of Case 4 all of the patients could indicate above chance that a left field terminal word was anomalous even if that word was semantically related either to a previous word or the expected completion of the sentence. Thus whether the accurate sense/nonsense judgements were based on lexical association or the appreciation of syntactic structure and semantic content, there appears to be a dissociation between the behavioural and electrophysiological indicators of meaning.

A similar dissociation was observed by Milberg and Blumstein in investigations of semantic priming in aphasics. Of relevance here is their finding that Wernicke's aphasics exhibited large semantic priming effects in both auditory and visual lexical decision tasks in the face of severe comprehension deficits, whereas Broca's aphasics with almost no comprehension deficits exhibited small priming effects in the auditory modality and none in the visual modality (Milberg and Blumstein, 1981; Blumstein *et al.*, 1982). A related dissociation between the ability to comprehend syntactically-constrained sentences and the ability to judge their grammaticality has also been observed for agrammatic aphasics (e.g., Linebarger *et al.*, 1983) and Case 3 (Baynes and Gazzaniga, 1988). In both instances, patients who could not comprehend semantically reversible active and passive sentences with sufficient accuracy to choose an appropriate pictorial representation were nonetheless able to judge whether the sentences were grammatical or not.

The finding that N400 could only be elicited by right hemisphere anomalies in patients who either showed overt right hemisphere speech (Case 1) or were on the way to developing it (Case 2) might indicate that a hemisphere can best subserve language generation if it contains a semantic organization that permits semantic priming to occur. Typically, discussions of the role of semantic priming in language processing have focused on comprehension (in particular, during reading and listening) rather than on production. This has been true despite the belief of some investigators that lexical spreading activation can be disregarded as a fundamental mechanism for facilitating lexical access in the reading of sentences (e.g., Henderson, 1982). In so far as it has been investigated, the same variables (e.g., concreteness, frequency, semantic relatedness) that influence lexical access and semantic priming in comprehension also exert similar effects during production—for example, by shortening the latency to speech onset (Taylor, 1969; Rosenberg, 1977). Moreover, there is evidence to indicate that semantically primed words can, on occasion, influence the order in which words in a particular sentence are uttered (Bock, 1986).

Clearly, further experiments need to be carried out to clarify the relationship between semantic priming operations and language production, both spoken and written. Nonetheless, we view our data as consistent with the hypothesis that semantic priming might play a crucial role in successful language output. Within the split-brain population, this proposition would lead to the prediction that the right hemispheres of Cases 1 and 2 would yield strong semantic priming effects whereas those of Cases 3–5 would not. In so far as evidence is available, this appears to be the case (Zaidel, 1983; Baynes and Gazzaniga, 1988). Whatever the nature of the priming/speech production turns out to be, the present results suggest that a hemisphere which can subserve speech has a different functional organization of the semantic lexicon than does a hemisphere which cannot.

Since the split-brain surgery in Cases 1 and 2 left their anterior commissures intact, the possibility must be considered that visual information presented to the right hemisphere might be transferred to the left for the production of linguistic and/or ERP responses. A recent MRI examination in Case 2 further shows the presence of some remaining callosal fibres in the rostral and splenial regions

(Gazzaniga *et al.*, 1984). Behavioural tests in both patients, however, showed an inability to cross-compare 2 visual patterns (i.e., judge them same or different) when presented separately to the left and right visual fields (Gazzaniga, 1987). This suggests that the word stimuli used in the present study were lateralized to the directly stimulated hemisphere.

Several recent reports have argued that split-brain patients can cross-integrate some visual information. For example, Ramachandran *et al.* (1986) reported that the split-brain patient was capable of perceiving apparent motion when the 2 visual stimuli were flashed alternately, one to each half brain. Likewise, Sergent (1983, 1986) reported that J.W., N.G. and L.B. (Cases 3–5 in the present study) could indicate whether 2 letters, 1 in each visual field, included a vowel or not. She interpreted their ability to produce a single response in the face of contradictory information as evidence for integration in the brainstem. Gazzaniga (1987), however, has argued that Sergent's results can be interpreted without invoking interhemispheric integration. Whatever the explanation, there is general agreement that only rudimentary visual information is transferred between the hemispheres of a split-brain patient, even those with anterior commissures intact (e.g., Holtzman, 1984).

It should also be noted that Case 3 has an intact anterior commissure and showed no evidence either of an interhemispheric visual matching capability or of vocal responses to left-field stimuli except under certain conditions. Specifically, he can report verbally which of 2 stimuli were flashed to his right hemisphere as long as both the stimulus and response options are binary (Gazzaniga *et al.*, 1987). Despite this ability, however, he cannot indicate whether 2 numbers flashed simultaneously 1 to each hemisphere are the same or different or report verbally the outcome of any operations performed on the contents of information presented to the left visual field. Whether such information transmission between the hemispheres is mediated by the anterior commissure or brainstem is unknown; however, it is clear that the nature of the information transmitted in this manner is relatively limited in detail.

These ERP recordings from the commissurotomy patients shed some light on the nature of the cerebral generators of the N400 component. In normal subjects the N400 typically has a widespread bilateral scalp distribution, with a slight tendency to be higher in amplitude and more prolonged over the right hemisphere (Kutas and Hillyard, 1982, 1983; Kutas *et al.*, 1988). In the present experiment, the N400 also had a bilateral distribution regardless of the field of presentation. Surprisingly, there was no consistent shift in the lateral distribution of the N400 as a function of the visual field receiving the anomaly either for the control or the commissurotomized subjects. Although the individual patients differed somewhat in the degree and direction of N400 asymmetry, these data are difficult to reconcile with the idea of independent cortical generators for the N400 in each of the cerebral hemispheres. Two alternative mechanisms seem reasonable to consider: first, it may be that the N400 is generated by deep structures within the stimulated hemisphere in such a way that a unilateral activation produces a bilateral scalp field. This view is consistent with the reports of depth recorded N400-like activity localized to subcortical generators within anterior temporal lobes (McCarthy and Wood, 1984; Smith *et al.*, 1986). In this case the slight right hemisphere preponderance of the N400 generally observed with normal subjects might reflect the contribution of a deep medial source in the left hemisphere orientated so as to make the potentials at the right scalp appear more negative than those at the left scalp. A second possibility would be that the scalp-recorded N400 emanates from bilateral activation of the cerebral hemispheres for anomalies presented to either hemisphere. According to this view, semantic analyses of anomalous words performed separately in either hemisphere of Cases 1 and 2 would trigger the activation of a common bilateral system (presumably via subcortical pathways), which then gives rise to the N400 recorded at the scalp.

The ERPs elicited on the trials where an anomalous word was presented to both visual fields simultaneously provide further evidence against there being independent generators for N400 in each hemisphere. If each hemisphere generated an N400 wave independently according to the type of word seen, the N400 difference wave to the bilateral anomalies should constitute a simple summation of the amplitudes of the difference waves engendered by the single right and left field anomalies. This clearly was not the case in either the split-brain subjects or the normal controls (*see* fig. 4). Indeed, in Cases 1, 3 and 4, the N400 difference wave was smaller for the bilateral anomalies than for the summed unilateral responses; in Case 3 the bilateral difference wave was also delayed. This is a puzzling result that suggests considerable interhemispheric interaction in the production of N400, perhaps including some interference between the hemispheres in these patients. The presence of a somewhat larger N400 in response to bilateral anomalies may reflect the partial cancellation of the N400 to unilateral anomalies by the positivity elicited by the congruous words simultaneously flashed to the other visual field. The observed ERP pattern for bilateral anomalies in the patients and controls is consistent with the view that the N400 arises from (or is dependent upon) a bilaterally projecting system that can be activated fully by semantic processing in either hemisphere for Cases 1 and 2, but only by processing events within the left hemisphere alone for the others. Future research may help to differentiate between these alternative generator proposals.

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# THE LAMBERT-EATON MYASTHENIC SYNDROME

## A REVIEW OF 50 CASES

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## SUMMARY

The clinical and electrophysiological features of 50 consecutive patients with the Lambert-Eaton myasthenic syndrome (LEMS) have been analysed. Carcinoma was detected (CD group) in 25, of whom 21 had small cell lung cancer (SCLC). SCLC was evident within 2 yrs of onset of LEMS symptoms in 20/21 cases, and at 3.8 yrs in 1/21. In the cases in whom no carcinoma was detected (NCD group), 14/25 had a history of LEMS > 5 yrs. The dominant neurological features were similar in the CD and NCD groups, and consisted of proximal lower limb weakness (100%), depressed tendon reflexes (92%) with posttetanic potentiation (78%), autonomic features, especially dryness of the mouth (74%) and mild/moderate ptosis (54%). The compound evoked muscle action potential amplitude in abductor digiti minimi was below the lower limit of control values in 48/50, and the increment following maximum voluntary contraction above the upper limit of control values in 48/50. Single fibre electromyographic abnormalities were found in 29/29 cases.

The analysis indicates that a patient presenting with LEMS has a 62% risk of an underlying SCLC, and that this risk declines sharply after 2 yrs, becoming very low at 4 to 5 yrs. It is argued that in SCLC cases antigenic determinants on tumour cells initiate the autoimmune response, often early in the course of the malignancy, but that the association of LEMS with tumours other than SCLC may be fortuitous. In the latter, and in NCD patients, the initiating factor(s) are unknown.

## INTRODUCTION

The Lambert-Eaton myasthenic syndrome (LEMS) is a disorder of neuromuscular transmission, first recognized clinically in association with lung cancer (Anderson *et al.*, 1953; Henson, 1953), and subsequently in cases in which no neoplasm was detected. Its pathophysiology has been elucidated by Lambert and his colleagues (Lambert *et al.*, 1956, 1961; Rooke *et al.*, 1960; Lambert and Rooke, 1965). Clinical electromyography revealed an abnormally small amplitude of the resting compound muscle action potential (CMAP) that increased progressively during high frequency (> 10 Hz) repetitive supramaximal nerve stimulation, or immediately following a short period of maximum voluntary contraction of the

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muscle. Studies by Elmqvist and Lambert (1968) and Lambert and Elmqvist (1971) on biopsied intercostal muscle from LEMS patients established that the abnormality was presynaptic, characterized by a decrease in the number of packets of transmitter (quanta) released by each nerve impulse. This was confirmed by pharmacological studies in which acetylcholine was measured by pyrolysis-mass fragmentography (Molenaar *et al.*, 1982). Transmitter release from biopsied LEMS intercostal muscle in response to nerve stimulation or depolarization by $K^+$ was reduced compared with controls, as was the resting nonquantal 'molecular leakage' of acetylcholine. By contrast, frequency of spontaneous transmitter release (i.e., miniature endplate potential frequency), was not significantly affected in LEMS (Lambert and Elmqvist, 1971).

The occasional association of noncarcinomatous LEMS with other autoimmune disorders (Gutmann *et al.*, 1972) raised the possibility of an autoimmune aetiology, which has now been substantiated both in carcinomatous and noncarcinomatous LEMS. In both, plasma exchange produced a short-term improvement (Newsom-Davis and Murray, 1984) and the IgG fraction of LEMS plasma injected intraperitoneally into mice transferred not only the physiological abnormalities (Lang *et al.*, 1981, 1983; Kim, 1985; Prior *et al.*, 1985), but also the characteristic morphological changes revealed by freeze-fracture electron microscopy of LEMS muscle (Fukunaga *et al.*, 1982), namely a reduction in the number of presynaptic active zones and active zone particles that are believed to represent voltage-gated calcium channels (VGCCs) (Fukunaga *et al.*, 1983). Electrophysiological studies of the effects of injected LEMS IgG on the quantal content of the endplate potential and on miniature endplate potential frequencies over a range of extracellular $Ca^{2+}$ concentrations provided functional evidence of a reduced number of VGCCs (Lang *et al.*, 1984, 1987). Loss of VGCCs would result in reduced $Ca^{2+}$ entry during nerve terminal depolarization and thus a decrease in transmitter release.

In a series of papers (Lambert *et al.*, 1956, 1961; Eaton and Lambert, 1957; Rooke *et al.*, 1960; Lambert and Rooke, 1965), Lambert and his colleagues reported the electromyographic abnormalities and clinical findings in LEMS patients. The present study was undertaken to analyse the clinical, electrophysiological and immunological features in a large group of patients in the light of the recent evidence for an underlying autoimmune mechanism, and to investigate further the association with lung cancer and its possible role in the aetiology of the disorder.

## PATIENTS AND METHODS

This study is based on 50 patients seen consecutively by one of us (J.N.D.) over the period 1978–1986, in whom a diagnosis of LEMS was made on the clinical findings and on electromyographic evidence of impaired neuromuscular transmission.

The clinical features described were obtained from a review of the case records. Two patients were investigated at the Royal Free Hospital, London, and the remainder at the National Hospital for Nervous Diseases, Queen Square.

The 48 patients seen at the National Hospital had electrophysiological studies performed by N.M.F.M. Repetitive stimulation was performed with surface stimulating electrodes. The compound muscle action potential (CMAP) was recorded with Ag/AgCl disc recording electrodes taped over the muscle belly and tendon insertion. In all cases the right ulnar nerve was stimulated at the wrist with the recording electrodes over abductor digiti minimi (ADM). Trains of 8 to 10 stimuli were initially delivered at 1 Hz and 3 Hz, and again at 3 Hz, 3 s after a period of maximum voluntary contraction of the muscle. In 29 cases, the CMAP was also recorded during 20 Hz stimulation. Values cited in the text are peak-to-peak amplitudes.

Motor and sensory nerve conduction studies were performed according to standard techniques. A concentric needle electrode was used for muscle sampling; single fibre electromyography (SFEMG) was undertaken on the extensor digitorum communis, sampling usually with a Medelec SF25 needle electrode.

Control values for repetitive stimulation were obtained from 20 healthy individuals (age range 18-56 yrs).

## RESULTS

Twenty-five patients had a history of malignancy (carcinoma detected—CD group) and 25 patients did not (no carcinoma detected—NCD group). All patients in the latter (NCD) group had sputum cytology and a chest x-ray undertaken initially; 12 also had a computerized tomographic (CT) lung scan and 4 underwent bronchoscopy. The chest x-ray had also remained normal during follow-up. The follow-up period in this group was greater than 5 yrs in 14 cases (fig. 1), and was greater than 10 yrs in 2.

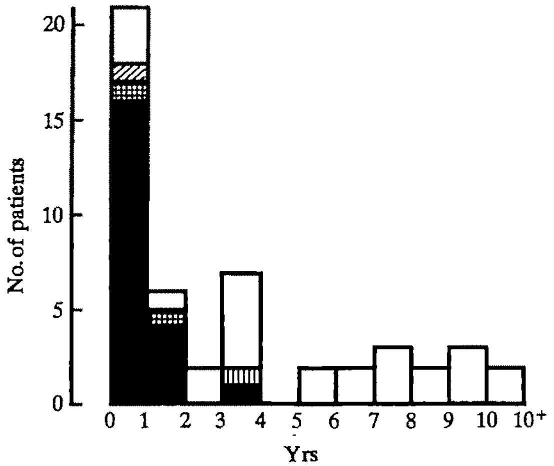

FIG 1 Duration of symptoms of LEMS at time of tumour detection in the CD patients and at final follow-up in NCD patients Solid bars = small cell lung carcinoma; vertical hatching = breast carcinoma; horizontal and vertical hatching = thoracic tumour of undetermined histology, open bars = NCD patients. Tumour diagnosis preceded symptoms of LEMS by 2 months in the case with adenocarcinoma, but the result has been included in the data for yr 1.

### *Age at onset*

The age at onset of neurological symptoms ranged between 17 and 79 yrs with a median of 54 yrs. Fig. 2 shows the distribution for all patients, and for the CD and NCD groups considered separately. Four patients (8%), all in the NCD group, were less than 30 yrs old at onset. Age at onset was otherwise similar in the two subgroups, respectively. Overall, 84% of patients were over the age of 40 yrs at onset of symptoms.

### *Race and sex*

All patients were Caucasian. There was a male predominance; in the CD group there were 14 males and 11 females while in the NCD group there were 18 males and 7 females. This difference was significant ($P < 0.05$) for the NCD group ($\chi^2 = 4.88$) and for the two groups considered together ($\chi^2 = 3.94$).

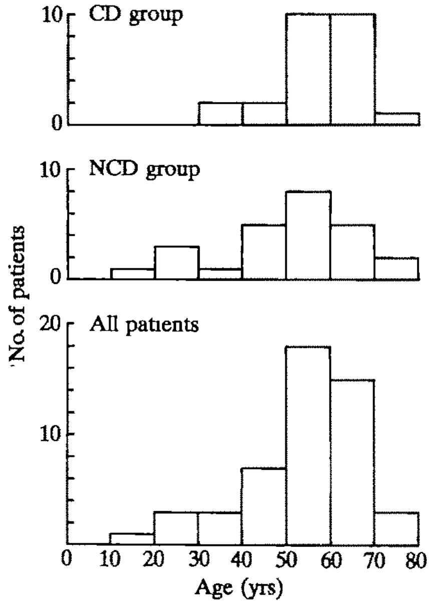

FIG. 2. Age at onset of symptoms of LEMS. CD = carcinoma detected; NCD = no carcinoma detected.

### *Features relating to the carcinoma*

*Tumour type.* The tumour was within the thoracic cavity in 24 of the 25 patients in the CD group. In 21 the histology was that of SCLC, poorly differentiated in 5 cases; histology was unavailable in 2 and 1 had an adenocarcinoma. The single patient in the CD group without a detectable thoracic tumour developed symptoms of LEMS 4 yrs before discovery and successful treatment of a breast carcinoma.

Additional neoplasms occurred in 3 of the 24 patients with intrathoracic tumours. In 1 patient (Appendix, Case 1) a lymphosarcoma (reticulum cell sarcoma) had been successfully treated 6 yrs before the onset of LEMS. A second patient (Appendix, Case 2) had successful treatment of 2 separate intraduct breast carcinomas 16 and 7 yrs before the onset of LEMS. The third patient developed LEMS 1.5 yrs before the discovery of SCLC, and at autopsy was found also to have a pancreatic adenocarcinoma.

*Smoking history.* Only 4 CD patients were nonsmokers. The underlying malignancies in these cases were SCLC (2), breast carcinoma (1), and adenocarcinoma of lung (1). One patient was a cigar smoker and 2 were reformed smokers (no tobacco intake for at least 10 yrs preceding tumour diagnosis). The remaining 18 patients (72%), all with thoracic cavity tumours, were regular smokers with a mean consumption of 24 cigarettes per day. By contrast, only 9 (36%) of the NCD group were regular or recently reformed smokers with a mean consumption of 18 cigarettes daily ($\chi^2 = 24.4$, $P < 0.001$).

*Time relationship with the onset of LEMS.* Symptoms of LEMS preceded diagnosis of the tumour by 5 months to 3.8 yrs (median 10 months) in 17 of the 24 patients with an intrathoracic malignancy, and were concurrent in 6. Only in 1 case did tumour diagnosis (adenocarcinoma of the lung) occur first, by an interval of 2 months. Fig. 1 shows that in 16 of the 21 cases with histologically proven SCLC, the tumour became evident within 1 yr of the onset of LEMS symptoms, and in 20/21 within 2 yrs.

*Presenting features of intrathoracic tumours.* In 14 of the 24 patients, the tumour presented with respiratory symptoms and/or signs, and the chest x-ray was found to be abnormal. In 9 patients an asymptomatic mass was noted on a routine chest x-ray. In 1 patient (Appendix, Case 3), who had had symptoms of LEMS for 1.9 yrs, SCLC was detected at autopsy after the patient presented terminally with dyspnoea (normal chest x-ray), increasing limb weakness and a rapidly enlarging liver. A similar increase in LEMS symptoms occurring at the time the tumour presented was noted in 1 other patient.

Other presenting features included: cerebellar degeneration syndrome (3) without evidence (CT scan) of cerebellar metastasis, inappropriate antidiuretic hormone production (2), skin hyperpigmentation (2), Cushing's syndrome (1), finger clubbing (1) and gynaecomastia (1). The patient with clubbing had an adenocarcinoma and in 1 of the patients with a cerebellar syndrome the tumour histology was unknown. The remainder of the patients had SCLC.

### *Associated immunological disorders in patients and relatives*

Thirteen patients (6 CD, 7 NCD) had a past history and 7 patients (1 CD, 6 NCD) a family history (first and second degree relatives) of an organ-specific autoimmune disease: thyrotoxicosis, hypothyroidism due to thyroiditis, vitiligo, pernicious anaemia, coeliac disease and juvenile-onset diabetes mellitus (Table 1). In all, 34% of patients had a past and/or family history of these diseases. Some patients (*see* Appendix, Case 4) had more than one autoimmune disease. Appendix Cases 4–7 illustrate these associations. Other similarly associated immunological diseases included rheumatoid arthritis (4), psoriasis (2), ulcerative colitis (1), scleroderma (1) and multiple sclerosis (1).

### *Diagnosis*

The initial diagnosis was correct in only 46% of cases. Myasthenia gravis was the commonest alternative diagnosis (10 cases); 2 underwent thymectomy, and histology (available in 1) showed thymus atrophy.

For all patients the median interval between onset of symptoms and diagnosis of LEMS was 8 months (range 1 month–13.6 yrs). The duration of symptoms before diagnosis was much longer for the NCD group (median 1.4 yrs) than for the CD group (median 6 months), this difference being statistically significant ($P < 0.03$; Mann-Whitney test).

TABLE 1 INCIDENCE OF ORGAN-SPECIFIC AUTOIMMUNE DISEASE

| *Disease* | *CD group* (*n* = *25*) | | *NCD group* (*n* = *25*) | | *All patients* (*n* = *50*) | |
|---|---|---|---|---|---|---|
| | PH | FH | PH | FH | PH | FH |
| Thyroid disease | 3 | 1 | 1 | 3 | 4 | 4 |
| Vitiligo | 3 | 0 | 2 | 0 | 5 | 0 |
| Pernicious anaemia | 0 | 0 | 3 | 1 | 3 | 1 |
| Coeliac disease | 0 | 0 | 2 | 1 | 2 | 1 |
| Juvenile-onset diabetes | 0 | 0 | 1 | 1 | 1 | 1 |

PH = past history; FH = family history.

### *Symptoms*

The presenting symptom was leg weakness in 62%, generalized weakness in 12%, arm weakness in 2%, aching and stiffness of muscles (either alone (12%) or with weakness (6%)) and autonomic dysfunction (impotence, dry mouth, constipation) in 6%. In most patients the onset was gradual, but in a few it was acute.

Symptoms occurring during the course of the illness are given in Table 2. Lower limb weakness was experienced in all cases, particularly affecting the ability to run or walk, to climb stairs or rise from a chair; 36% developed aching muscles and/or stiffness that was often increased by exercise.

Upper limb weakness (78% of all patients) was usually mild compared with that in the lower limbs, and affected proximal muscles particularly; only a few noticed distal weakness. Patients were often aware of a fatiguable element in their weakness, for example after prolonged exercise. Perhaps because of this, symptoms often seemed excessive for the degree of weakness observed on examination. In 22% symptoms were worse in hot weather or after a hot bath.

Symptoms of autonomic dysfunction were experienced by 80% of patients, the most common being a dry mouth (74%) and impotence (41% males). Less common complaints were constipation (Appendix, Case 7), blurred vision and impaired sweating (Appendix, Case 8).

TABLE 2 SYMPTOMS DURING THE COURSE OF THE ILLNESS

| | *No. of patients* | | |
|---|---|---|---|
| *Symptom* | *CD group* (*n*(%)) | *NCD group* (*n*(%)) | *All patients* (*n*(%)) |
| Lower limb weakness | 25 (100) | 25 (100) | 50 (100) |
| Upper limb weakness | 17 (68) | 22 (88) | 39 (78) |
| Factors exacerbating limb weakness | 12 (48) | 20 (81) | 32 (64) |
| Prolonged exercise | 12 | 19 | 31 |
| Hot bath/hot weather | 2 | 9 | 11 |
| Muscle ache/pain/stiffness | 8 (32) | 10 (40) | 18 (36) |
| Autonomic symptoms | 16 (64) | 24 (96) | 40 (80) |
| Dry mouth | 16 | 21 | 37 |
| Impaired sexual function (failure of erection/ejaculation) | 3 | 10 | 13 |
| Constipation | 2 | 7 | 9 |
| Blurred vision | 2 | 2 | 4 |
| Impaired sweating | — | 2 | 2 |
| Cranial nerve symptoms | 16 (64) | 19 (76) | 35 (70) |
| Diplopia | 11 | 14 | 25 |
| Drooping eyelids | 10 | 11 | 21 |
| Slurred speech | 4 | 8 | 12 |
| Difficulty swallowing | 5 | 7 | 12 |
| Difficulty chewing | 4 | 4 | 8 |
| Head lolling | 3 | 4 | 7 |
| Voice weaker | 4 | 2 | 5 |
| Sensory complaints | 4 (16) | 2 (8) | 6 (12) |
| Low back pain | 2 | 1 | 3 |
| Numbness/parasthesiae of extremities | 3 | 1 | 4 |
| Respiratory distress requiring artificial ventilation | 2 (8) | 1 (4) | 3 (6) |
| Spontaneous | 1 | — | 1 |
| Induced by anaesthesia | 1 | 1 | 2 |
| Weight loss | 5 (20) | 7 (28) | 12 (24) |
| Preceding viral-type illness | 3 (12) | 5 (20) | 8 (16) |

Cranial nerve symptoms, usually mild and often transient, were experienced by 70% of patients, diplopia and drooping of the eyelids being the most common. Numbness and/or paraesthesiae of the extremities were uncommon complaints.

Three patients developed respiratory distress requiring artificial ventilation. In 1 patient this occurred spontaneously (Appendix, Case 3), whereas in the other 2 cases it followed anaesthesia (*see*, e.g., Appendix, Case 1). Occasionally, symptoms of LEMS were preceded by a viral-type illness (Appendix, Cases 1, 9).

No features were identified distinguishing CD and NCD cases on the basis of neurological symptoms; even the incidence of weight loss was approximately equal in the two groups.

### *Signs*

Table 3 lists the patients' signs at the time that they were seen by us. Muscle weakness was characteristically present proximally, especially affecting the lower limbs. In only 2 cases were the upper limbs weaker than the lower limbs or distal muscles weaker than proximal ones. Progressive augmentation of strength during the first few seconds of sustained maximum effort was a prominent feature, and was also detected on repeat testing of an individual muscle over several seconds. Continued testing usually produced fatigue with increasing weakness. Muscle wasting was noted in only 4 patients and was usually mild.

TABLE 3. SIGNS

| *Signs* | *CD group* (*n* (%)) | *NCD group* (*n* (%)) | *All patients* (*n* (%)) |
|---|---|---|---|
| Cranial nerve signs | 15 (60) | 16 (64) | 31 (62) |
| Ptosis | 13 | 14 | 27 |
| Jaw weakness | 1 | 1 | 2 |
| Facial weakness | 4 | 4 | 8 |
| Palatal weakness | — | 9 | 4 |
| Neck weakness | 8 | 9 | 17 |
| Muscle wasting | 1 (4) | 3 (12) | 4 (8) |
| Muscle weakness | 22 (88) | 24 (96) | 46 (92) |
| Lower limbs | 22 | 24 | 45 |
| Proximal | 22 | 23 | 45 |
| Distal | 5 | 2 | 7 |
| Upper limbs | 18 | 24 | 41 |
| Proximal | 18 | 23 | 41 |
| Distal | 7 | 8 | 15 |
| Reflexes | | | |
| Normal | 1 (4) | 3 (6) | 4 (8) |
| Depressed or absent | 24 (96) | 22 (88) | 46 (92) |
| Posttetanic potentiation | 20 (80) | 19 (76) | 39 (78) |
| Sensory impairment | 2 (8) | — | 2 (4) |
| Diminished lower limb vibration sense | 1 | — | 1 |
| Diminished lower limb light touch/pin prick | 1 | — | 1 |
| Autonomic signs | 3 (12) | 3 (12) | 6 (12) |
| Sluggish pupillary reaction to light | 3 | 3 | 6 |
| Absent sweating (sweat test) | — | 1 | 1 |

Limb reflexes were depressed or absent in 92 %, but in 78 % of cases there was clear potentiation of one or more reflexes after a sustained (10–15 s) maximum voluntary contraction of the muscle being tested.

The dominant cranial nerve sign was ptosis (fig. 3), present in 54% cases; weakness of neck flexion was also relatively common. Despite the frequency of transient diplopia as a complaint, clinical evidence of external ophthalmoplegia was not observed. Sensory impairment, unexplained by other causes, was found in only 2 patients, both in the CD group.

Signs of autonomic dysfunction were seen in 6 cases (12%) with a sluggish pupillary reaction to light being present in all of them. The 2 patients tested with dilute pilocarpine (1 case) or methacholine (1 case) showed evidence of postganglionic denervation hypersensitivity.

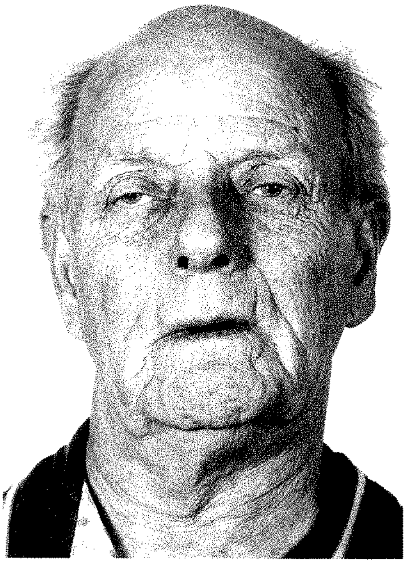

FIG. 3. Bilateral ptosis in a 72-yr-old patient in whom no carcinoma was detected (*Appendix*, *Case 8*).

No pattern of neurological signs was found that distinguished between the CD and NCD groups. Muscle weakness was typically more extensive and of greater severity in patients with a longer disease duration before diagnosis, although this was certainly not true in all cases.

*Laboratory investigations*

An ESR was obtained at the time of our initial assessment in all CD patients, and in 24/25 of the NCD group. The mean values in the two groups were 21 (SD ± 20) and 8 (SD ± 7), respectively, this difference being statistically significant ($P < 0.01$; Mann-Whitney test). The highest recorded ESR in the NCD group was 27 mm/h.

Serum T4 estimations, available for 20/25 CD patients and 25/26 NCD patients, were all normal. Serum creatine kinase levels were also normal in all patients on whom the test was performed (21/25 CD; 21/25 NCD).

Immunoglobulin abnormalities were found in 4 patients. Two CD patients had an IgG kappa paraprotein detectable in the serum. One of the NCD patients had a polyclonal IgG increase (Appendix, Case 9) and another, with adult-onset coeliac disease, had a low IgA level.

A serum autoantibody screen including anti-acetylcholine receptor (AChR) antibody (measured by a radioimmunoassay using $^{125}$I-alpha-bungarotoxin labelled human AChR; *see* Vincent and Newsom-Davis, 1985) was performed in all patients (Table 4). Organ-specific (thyroid, stomach, skeletal muscle) autoantibodies were detected in 34% of all patients (6 CD, 24%; 11 NCD, 44%) and non-organ-specific antibodies in 42% (15 CD, 60%; 7 NCD, 24%). Serum anti-AChR antibody was detected in none. Organ-specific autoantibodies were sometimes present in patients without past or family history of autoimmune disease. In all, 26 patients (52%) had a past or family history of organ-specific autoimmune disease and/or detectable serum autoantibodies.

TABLE 4 INCIDENCE OF AUTOANTIBODIES

| *Autoantibody* | *CD group (n = 25)* | *NCD group (n = 25)* | *All patients (n = 50)* |
|---|---|---|---|
| Organ specific | | | |
| Thyroid | | | |
| Microsomal | 3 | 5 | 8 |
| Thyroglobulin | 0 | 2 | 2 |
| Stomach | | | |
| Gastric parietal cell | 0 | 6 | 6 |
| Skeletal muscle | | | |
| Acetylcholine receptor | 0 | 0 | 0 |
| Striated muscle | 3 | 3 | 6 |
| More than one type of autoantibody | 0 | 4 | 4 |
| Nonorgan specific | | | |
| Antinuclear (titre ⩾ 1/40) | 9 | 4 | 13 |
| Smooth muscle | 5 | 2 | 7 |
| Mitochondrial | 3 | 1 | 4 |
| Rheumatoid factor | 2 | 0 | 2 |

An i.v. edrophonium (Tensilon) test was performed on 21 patients (5 CD, 16 NCD); in all but 2 this was undertaken at the referring hospital. It was reported as negative in 5 patients (including the 2 cases studied by us), equivocal in 2 and subjectively or objectively positive in 14.

A muscle biopsy had been carried out in 9 cases in whom there was initial diagnostic uncertainty. Type II fibre atrophy was seen in 6 patients. In the others the changes were reported as nonspecific, but the histology was not available for review.

### *Electrophysiological studies*

Most cases were not receiving medication. Exceptions were 2 NCD patients receiving oral corticosteroids, and 5 CD patients who had recently begun radiotherapy and/or chemotherapy for their tumours. Sensory action potentials were reduced in 1 patient (insulin-dependent diabetes mellitus) and absent in another (sensorimotor axonal neuropathy associated with vincristine therapy). Motor conduction velocities were normal except in these 2 patients in whom they were marginally reduced.

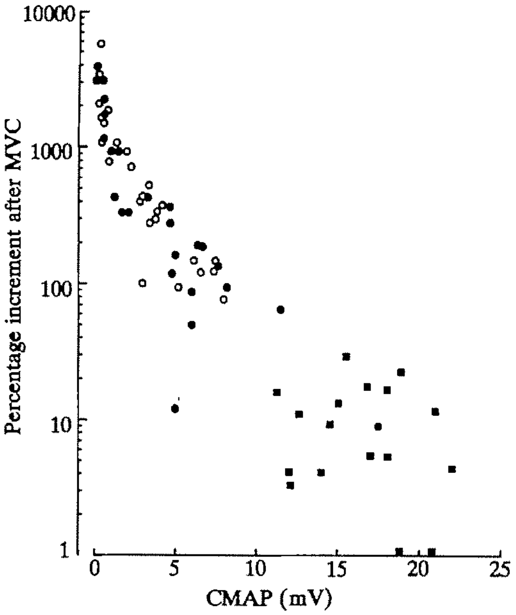

FIG. 4 Electrophysiological findings in LEMS patients (filled circles = CD; open circles = NCD) and in control subjects (filled squares). CMAP = compound muscle action potential; MVC, maximum voluntary contraction for 10–15 s. Two control subjects showed no increment following MVC (initial CMAPs 23.0 and 15.0 mV, respectively) and 1 showed a 10.7% decrement (initial CMAP 8.4 mV); these results are not included in the figure.

Fig. 4 plots values for the initial CMAP amplitude recorded from ADM, against the log percentage increment after 15 s maximum voluntary contraction in patients and controls. The mean initial CMAP amplitude for controls was 16.2 SD ± 3.8 mV, whereas that for patients was 3.7 SD ± 3.4 mV. In only 2 patients was the initial CMAP amplitude greater than the minimum value (8.4 mV) recorded from controls. In both, the diagnosis was made on the basis of typical clinical features and increased jitter and blocking on single fibre EMG; the history of one is given in the Appendix (Case 10).

In the CD group, the mean initial CMAP amplitude (4.3 SD ± 4.1 mV) was slightly higher than in the NCD group (3.2 SD ± 2.4 mV) but this difference was not significant. There was, however, a statistically significant difference ($P < 0.02$, Mann-Whitney test) between the mean initial CMAP amplitude in those patients with a disease duration of less than one year before the time of EMG diagnosis (26 cases; mean CMAP amplitude, 4.8 SD ± 3.8 mV) and those in whom there was a longer disease duration prior to diagnosis (24 cases; mean CMAP amplitude, 2.5 SD ± 2.4 mV).

The mean amplitude of the CMAP in ADM increased from 3.7 SD ± 2.4 mV to 13.6 SD±4.8 mV following 15 s maximum voluntary contraction in LEMS patients (mean increment 890%) whereas in controls the value increased to 17.6 SD±4.4 mV (mean increment of 9%). In only 2 patients (including Appendix Case 10) was the percentage increment in CMAP amplitude less than the maximum increment (24%) in controls.

In the 29 patients in whom the test was performed, repetitive stimulation of the ulnar nerve at a rate of 20 Hz produced a mean increment in the CMAP amplitude of 854 SD±1138% (range: 20–4774%), the mean value being similar to that seen following 15s maximum voluntary contraction. Stimulation at 20 Hz was performed in the 2 patients in whom the percentage increment following 15 s maximum voluntary contraction was $< 25\%$; in 1, the resulting increment (50%) was clearly abnormal.

The response to repetitive stimulation at 3 Hz was tested in 49 patients. The initial CMAP from ADM in 2 cases was too small to detect a decrement. Of the remaining 47 patients, 43 had a maximum decrement $> 2\%$ (the maximum observed at 3 Hz stimulation in healthy controls). The mean decrement for the 47 patients was 27 SD±15%.

Motor unit sampling with a needle electrode was normal in 2 patients, showed neurogenic change in 1 (sensorimotor axonal neuropathy due to vincristine therapy) and was 'myopathic' in character in the remaining 42 patients in whom the test was performed. The myopathic picture was usually that of brief, spiky and sometimes polyphasic units in a pattern that was often initially reduced but which characteristically showed an increase in both the number and amplitude of units recruited during sustained muscle contraction.

Abnormal jitter and/or blocking were seen in all of the 29 cases who underwent single fibre EMG. Increased jitter was frequently observed in every potential examined in a muscle, and blockings were also very common. The effect of motor unit firing rate on stability of potentials was not systematically studied, but in several cases reduction in blocking and jitter was seen with increasing voluntary contraction of the muscle.

### *Prognosis*

No follow-up details were available for 1 of the 25 CD patients. The patient with breast carcinoma as her sole malignancy remains alive and apparently tumour-free 10 yrs after detection and treatment of the cancer. Of the remaining 23 patients with a thoracic cavity tumour, 18 have died, the median duration of the interval between tumour detection and death being 8.5 months, the mean 10 months (range 0–32 months). Three of the 5 surviving patients have had a clear response to treatment with no detectable tumour at 2.9, 3.5 and 4.2 yrs after tumour diagnosis. These 3 patients also had complete remission of LEMS symptoms.

No follow-up details were available on 1 of the patients from the NCD group. Three patients died from causes other than their disease 7 months, 3.7 and

16.7 yrs after onset of the LEMS. The remaining 21 patients remain alive at a median of 6.9 yrs (mean 6.1 yrs; range 11 months–14.3 yrs) from the onset of the LEMS.

## DISCUSSION

Small cell lung carcinoma is the tumour most commonly reported in association with LEMS. This tumour was present in 21 of the 23 CD patients in our series in whom histology was available. Similarly in the series of Lambert and Rooke (1965) SCLC was found in 17 of 30 patients. This tumour thus appears to have a special role in LEMS. SCLC is possibly of neural crest origin (Tischler *et al.*, 1977). Tumour cells are stained by the human neuroectodermal marker UJ13A (Allan *et al.*, 1983); they contain neurosecretory granules and are capable of releasing biologically active peptides such as antidiuretic hormone and adrenocorticotrophic hormone (Rees and Ratcliffe, 1974). Electrophysiological studies (McCann *et al.*, 1981) and $K^+$ stimulated (voltage dependent) $^{45}Ca^{2+}$ flux assays (Roberts *et al.*, 1985) on cultured human SCLC cell lines have demonstrated expression of functional VGCCs. Moreover, $K^+$ stimulated $Ca^{2+}$ flux is inhibited by LEMS IgG consistent with the presence of an anti-VGCC antibody (Roberts *et al.*, 1985). This suggested that the primary autoantibody response in SCLC cases was to VGCCs on the cancer cells, cross-reactivity of the antibody with similar VGCC determinants at motor nerve terminals leading to the neurological syndrome. In support of this is the observation that treatment of the primary tumour by excision, chemotherapy or deep x-ray often results in an improvement or remission of the neurological syndrome (Anderson *et al.*, 1953; Rooke *et al.*, 1960; Jenkyn *et al.*, 1980; Jablecki, 1984; present authors' unpublished observations).

What role, therefore, might non-SCLC tumours, present in 2 of our cases and in occasional single case reports, play in triggering the disorder? We suggest that these are chance associations in a population at risk for tumour development, by virtue of its age. Some of these cases may have an occult SCLC, while others may not. The recent finding of $K^+$ stimulated $Ca^{2+}$ flux in a range of different human SCLC cell lines that can be blocked by LEMS IgG, and its absence in squamous carcinoma and adenocarcinoma cell lines, lends support to this view (B. Lang, J. Gill, A. Vincent and J. Newsom-Davis, unpublished results).

Our analysis also strongly supports the view that a population of LEMS cases exists unassociated with SCLC. The longest interval between the onset of LEMS and x-ray evidence of tumour was 3.8 yrs in our series, and 2.3 yrs in Lambert's series (Lambert and Rooke, 1965); in the remainder of our cases the interval was less than 2 yrs. These figures are broadly in accord with the predicted value of 2.8 yrs for the interval between the initial malignant change and the radiological diagnosis of SCLC, assuming a tumour size of 3 cm at that time (Geddes, 1979). Thus the probability that an occult SCLC underlies LEMS in the 14 cases where the history exceeded 4 yrs would appear to be very low, unless SCLC doubling times were to be substantially lower in LEMS cases. The rarity of cases presenting with a LEMS-SCLC diagnostic interval exceeding 4 yrs argues against this, but this possibility cannot yet be excluded. Incidentally, the data also suggest that in the CD group the autoimmune response is usually triggered early in the course of malignancy.

Based on the outcome in those with evidence of an intrathoracic malignancy (excluding adenocarcinoma) and those in the NCD group who have a history of > 5 yrs, one can estimate that the risk of an underlying SCLC in a patient first presenting with LEMS is about 62%. This figure is less than that (70%) quoted by Elmqvist and Lambert (1968), but these authors included non-SCLC cases. The probability of an underlying SCLC declines sharply after 2 years (fig. 1), and appears to be very low after 4 yrs. Clinical features from our study that point to the presence of an underlying SCLC include a history of smoking, an otherwise unexplained increase in the ESR, and age at onset over 30 yrs. Our youngest CD patient was 34 yrs old and that in Lambert's series was 41. In addition, we have previously reported in a small series of cases that the proportion of OKT8$^+$ peripheral blood lymphocytes was strikingly reduced in SCLC associated cases compared with noncancer cases (Robb *et al.*, 1985).

Clinical features in our series were similar to those of Lambert and colleagues, notably proximal muscle weakness, dry mouth, erectile impotence and depressed tendon reflexes. Interestingly, 22% of patients volunteered that weakness was worse in hot weather or after a hot bath, a complaint not mentioned in previous reports. This accords with the previous finding that the defect in neuromuscular transmission in LEMS becomes more severe when the local temperature is raised (Ward and Murray, 1979). Importantly, with respect to the differential diagnosis of myasthenia gravis, ocular symptoms were common, and 54% of cases had mild to moderate bilateral ptosis, but in none was external ophthalmoplegia detected.

Rubenstein *et al.* (1979) drew attention to the symptoms of dry mouth, impaired lachrimation, impotence, blurred vision, constipation, difficulty with micturition and impaired sweating that were often reported by patients with LEMS, and that implied a specific cholinergic dysautonomia; 80% of our cases had one or more of these. The relatively common complaint of muscle aching, pain and stiffness, often aggravated by exercise (36% of cases), was noted by Wise and MacDermot (1962). Sensory symptoms were much less common in our patients (12%) than in Lambert's series (50%). As in myasthenia gravis, sensitivity of LEMS patients to muscle relaxants, especially succinycholine and d-tubocurarine, has been frequently reported in the literature (Anderson *et al.*, 1953; Lambert *et al.*, 1961; Brown and Johns, 1974). This occurred in 2 of our cases and resulted in prolonged apnoea. In another, spontaneous involvement of respiratory muscles led to acute ventilatory failure.

In 26% of our patients there was a past history of one or more organ-specific autoimmune diseases, and 34% had one or more organ-specific autoantibodies, the overall incidence of both being somewhat higher in the NCD group. These results are similar to those of Lennon *et al.* (1982). Her group obtained sera from

64 patients with LEMS and detected organ-specific autoantibodies in 45% of cases, as compared with only 17% of age-matched controls. The incidence of autoantibodies was much higher in patients with LEMS and no detectable tumour (52%) than in those with a known malignancy (28%).

The predominance of males affected (1.8:1 for all patients, 2.6:1 for NCD patients) was significant both for the patients as a whole and for the NCD group. Differences in sex incidence have also been observed in the clinical subgroups in myasthenia gravis (Compston *et al.*, 1980) which also differ with respect to their HLA associations. In LEMS, both CD and NCD patients showed a strong association with HLA-B8 and with the Ig heavy chain marker Glm(2) (Willcox *et al.*, 1985).

Two of our cases, who had evidence of impaired neuromuscular transmission on single fibre EMG, lacked an incremental response to MVC, and in 1 case, also to high frequency electrical stimulation. The diagnosis in the latter was based on the associated clinical features. In practice, tetanic stimulation added useful information in only 1 of our cases and, because it is painful, is probably best reserved for suspected cases where results of other electrophysiological tests are equivocal. In our series, increased jitter and blocking were the most sensitive indices of impairment, being present in all 29 cases tested. They appeared to be more prominent than in cases of myasthenia gravis of comparable weakness, but diminished with increasing firing rates, pointing to a presynaptic disorder of neuromuscular transmission.

Abnormal muscle biopsies have occasionally been reported in patients with LEMS (Vroom and Engel, 1969; Oh, 1972; Henriksson *et al.*, 1977), the usual pathological change being type II fibre atrophy. This was seen in the 6 patients from our series whose biopsies we reviewed. This abnormality, and also the mild proximal wasting observed clinically in 4 cases, was probably a consequence of disuse, exercise being limited because of muscle fatiguability.

LEMS is an uncommon condition and, even amongst patients with SCLC, the incidence of the neurological syndrome is probably less than 5% (Lambert and Rooke, 1965; Hawley *et al.*, 1980). It is therefore not surprising that in over half the patients the referral diagnosis was incorrect, the most common alternative diagnosis being myasthenia gravis. From our study, features favouring the diagnosis of LEMS are the relative absence of cranial nerve signs (apart from mild or moderate ptosis), the presence of dysautonomia (especially a dry mouth) and muscle pain, and decreased or absent tendon reflexes often with associated posttetanic potentiation. Response to edrophonium is often weak and antiacetylcholine receptor antibody is undetectable in serum.

The electrophysiological changes in LEMS are usually clear-cut, but occasional cases have been reported that appear to show an overlap between LEMS and myasthenia gravis (Takamori and Gutmann, 1971; Schwartz and Stålberg, 1975). Tabbaa *et al.* (1986) recently reported a patient with myasthenic weakness, dysautonomia, hypoactive reflexes, electrophysiological features consistent with both disorders, strongly positive acetylcholine receptor antibody and an invasive thymoma. Such overlap features were not observed in our own cases. An immunological approach will be required to establish unequivocally the coexistence of myasthenia gravis and LEMS. At present we lack a simple immunoassay for the specific antibody in LEMS. Antibody to VGCC can only be detected by complex biological assays in which plasma or IgG is tested either for its effects on electrophysiological transmission after injection into animals or for its ability to reduce $K^+$ stimulated $Ca^{2+}$ flux in cultured cell lines.

Neither the immunogenetic studies in LEMS, nor the electrophysiological changes and clinical features, analysed here, show any consistent differences between those who have an underlying SCLC and those who do not. Thus this disease which is homogeneous in its clinical expression has more than one triggering factor: in about 60% of cases this appears to be SCLC while in the remainder the factor(s) are unknown. These observations support the view that paraneoplastic neurological diseases may have apparently indistinguishable nonparaneoplastic counterparts (Arnason, 1979) and provide further evidence that a single autoimmune disease may have more than one initiating factor.

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## APPENDIX

In all Appendix cases, the examination and EMG findings are those recorded by us.

### *Case 1*

A.C., female, born 1924. 1975: lymphosarcoma (reticulum cell sarcoma) treated successfully with chemotherapy. December, 1981: viral pneumonia (fever and pleuritic chest pain) treated successfully with antibiotics. January 1982: confined to bed for 4 days with inability to move limbs; noticed tingling of the face, hands and feet. Later she became able to walk again but remained weak, numbness persisting in hands and feet. August 1982: right cataract extraction (general anaesthesia with scoline and curare) followed by 18 h of assisted ventilation because of prolonged apnoea and immobility. September 1982: ptosis, dry mouth and intermittent diplopia. Diagnosis of LEMS. Examination (October, 1982): bilateral ptosis, diplopia, moderate proximal limb weakness and mild distal lower limb weakness, depressed or absent tendon reflexes with posttetanic potentiation, subjective distal impairment of light touch. Investigations. microsomal thyroid antibody titre 1/1600. Abnormal chest x-ray and biopsy evidence of SCLC. EMG (October, 1982): initial CMAP 3.2 mV; 28% decrement at 3 Hz stimulation; CMAP following 15 s maximum voluntary contraction 17 mV (431% increment); increased jitter and blocking on single fibre EMG.

### *Case 2*

B.M., female, born 1926. 1966: left intraduct breast carcinoma treated successfully with surgery and radiotherapy. 1975: right intraduct breast carcinoma treated successfully with surgery. September, 1982: pain in right hip and increasing weakness and heaviness of both legs ultimately requiring assistance to walk. Examination (March, 1982): limb strength normal, depressed or absent tendon reflexes with posttetanic potentiation, skin hyperpigmentation. Abnormal chest x-ray and sputum cytology evidence of SCLC. Investigations. low serum sodium concentration secondary to inappropriate antidiuretic hormone production. EMG (March, 1982): initial CMAP 1.8 mV; no decrement at 3 Hz stimulation; CMAP following 15 s maximum voluntary contraction 7.8 mV (333% increment). Diagnosis of LEMS

### *Case 3*

M.C., female, born 1921. Past history of thyrotoxicosis. February, 1980: aching in thighs and tight feeling around ankles; weakness of legs with inability to rise unassisted from sitting. September, 1980: respiratory arrest at home, resuscitated by husband's 'kiss of life', low $pO_2$ and high $pCO_2$ on admission, intermittent ventilation in hospital until January, 1981. Examination (January, 1981) wasting of proximal musculature, moderate proximal limb weakness, depressed or absent tendon reflexes with no posttetanic potentiation, vital capacity less than 1.1. Investigations: EMG (January, 1981): initial CMAP 2.1 mV; 38% decrement at 3 Hz stimulation, CMAP following 15 s maximum voluntary contraction 9.1 mV (333% increment). Diagnosis of LEMS. September, 1981. dyspnoea and increased limb weakness. December, 1981: hepatomegaly; chest x-ray normal. January, 1982: autopsy evidence of right paratracheal SCLC and liver metastases.

### *Case 4*

C.J., male, born 1933. Past history of pernicious anaemia, family history of pernicious anaemia (maternal grandmother). December, 1977 stiffness in muscles and cramp-like feelings in legs, weakness with fatiguability limiting ability to rise from a chair, climb stairs or walk. Weakness worse in hot weather; intermittent diplopia, dry mouth, impaired erection and ejaculation. Diagnosis of LEMS. Examination (July, 1980): waddling gait, mild proximal lower limb weakness, depressed or absent tendon reflexes with posttetanic potentiation, vitiligo on forearms and penis. Investigations: parietal cell antibody positive, thyroglobulin antibody titre 1/320, microsomal antibody titre 1/6400. EMG (July, 1980): initial CMAP 0.4 mV, 20% decrement at 3 Hz stimulation, CMAP following 15 s maximum voluntary contraction 14 mV (3400% increment)

### *Case 5*

J.C., female, born 1948. Family history of pernicious anaemia (great aunt). September, 1978 general malaise and lower limb weakness with fatiguability limiting ability to rise unaided from kneeling or squatting, climb stairs or walk distances. Weakness worse after hot bath; intermittent heaviness of head so that she had to hold it up with her hands; dysarthria and dysphagia with nasal regurgitation of fluids; dry mouth. November, 1978: diagnosis of myasthenia gravis and adult-onset coeliac disease. Examination (February, 1979): waddling gait, dysphagia with nasal speech, bilateral facial weakness, reduced palatal movement, weakness neck flexion, generalized limb weakness worse proximally, depressed or absent tendon reflexes with posttetanic potentiation. Investigations. EMG (February, 1979): initial CMAP 0.5 mV; 32% decrement at 3 Hz stimulation, CMAP following 15 s maximum voluntary contraction 5.8 mV (1060% increment), increased jitter and blocking on SFEMG. Diagnosis of LEMS.

*Case 6*

R.S., male, born 1932. Family history of insulin-dependent diabetes mellitus (daughter). March, 1980: weakness and wasting of shoulder girdles limiting ability to play golf. Later developed lower limb weakness with fatiguability limiting ability to play squash, climb stairs or get out of a chair. Weakness worse in hot weather; dry mouth. Examination (December, 1981): wasting of shoulder girdles, moderately severe proximal weakness, mild weakness small hand muscles, tendon reflexes obtainable with reinforcement Investigations· EMG (December, 1981): initial CMAP 6 1 mV; 15% decrement at 3 Hz stimulation; CMAP following 15 s maximum voluntary contraction 15 mV (146% increment); increased jitter and blocking on SFEMG. Diagnosis of LEMS

*Case 7*

E.S., female, born 1914. Past history of hypothyroidism. May, 1984: colonoscopy for investigation of constipation. Next day, limb weakness with inability to walk, and a dry mouth, skin of mouth started to peel, heaviness of eyelids and dysphagia. Limb weakness improved with pyridostigmine and low dose prednisolone. September, 1984: diagnosis of LEMS. Examination (June, 1986). able to take a few steps using a walking stick, mild bilateral ptosis, mild weakness of eye closure and neck flexion, generalized limb weakness, worse proximally and in lower limbs, depressed or absent tendon reflexes with posttetanic potentiation. Investigations: striated muscle antibody positive; microsomal thyroid antibody titre 1/100. EMG (June, 1986): initial CMAP 0.9 mV, 5% decrement at 3 Hz stimulation; CMAP after 15 s maximum voluntary contraction 8 mV (789% increment); increased jitter and blocking on SFEMG.

*Case 8*

C.M , male, born 1912. December, 1981. blurred vision and drooping of eyelids, swaying when walking. July, 1982: diagnosis of LEMS. August, 1984: increasing muscle fatigue and cramp; difficulty supporting head in evening and turning in bed at night; dry mouth; absent sweating. Examination (November, 1984)· bilateral ptosis (fig. 3), sluggish pupillary reaction to light, power normal, depressed or absent tendon reflexes with posttetanic potentiation, absent sweating on a formal sweat test. Investigations. striated muscle antibody present in serum. EMG (October, 1984). initial CMAP 2.2 mV; 20% decrement at 3 Hz stimulation; CMAP after 15 s maximum voluntary contraction 18 mV (718% increment); increased jitter and blocking on SFEMG.

*Case 9*

G.P., male, born 1932. January 1981: upper respiratory tract infection. Several weeks later: lower limb weakness limiting ability to get out of chairs, climb stairs or walk; 1982· upper limb weakness, drooping left eyelid, impotence and intermittent diplopia. Thymectomy. July, 1983. Diagnosis of LEMS. Examination (November, 1983). waddling gait, bilateral ptosis, proximal muscle wasting and weakness, depressed or absent tendon reflexes with posttetanic potentiation. Investigations. serum IgG of 25 g/l (normal, 4–18) EMG (November, 1983). initial CMAP 7.4 mV; 47% decrement at 3 Hz stimulation; CMAP after 15 s maximum voluntary contraction 16.5 mV (123% increment); increased jitter and blocking on SFEMG.

*Case 10*

K.A., male, born 1930 October, 1983· dyspnoea and haemoptysis with abnormal chest x-ray; bronchoscopic biopsy evidence of SCLC Treatment with chemotherapy and palliative cranial radiotherapy. Also noticed increasing muscle weakness limiting ability to climb stairs and walk, dry mouth and impotence. Examination (March, 1984): generalized muscle weakness more marked proximally in upper limbs and distally in lower limbs, depressed or absent tendon reflexes with posttetanic potentiation. Investigations: EMG (March, 1984): initial CMAP 17.4 mV; no decrement at 3 Hz stimulation, CMAP following 15 s maximum voluntary contraction 19 mV (9% increment). June, 1984: well, apart from muscle weakness. EMG (June, 1984): initial CMAP 12.0 mV; 3% decrement at 3 Hz stimulation; CMAP after 15 s maximum voluntary contraction 14.5 mV (21% increment) and after 20 Hz stimulation 18 mV (50% increment); increased jitter and blocking. Diagnosis of LEMS

*Brain* (1988), **111**, 597-614

# DISSEMINATED CYSTICERCOSIS

## NEW OBSERVATIONS, INCLUDING CT SCAN FINDINGS AND EXPERIENCE WITH TREATMENT BY PRAZIQUANTEL

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## SUMMARY

Although the symptom complex of disseminated cysticercosis has been well recognized for over half a century, it is not clearly included in recent disease classifications. Three such patients are described whose main features were uncontrolled seizures, progressive dementia, behaviour disorder, muscular pseudohypertrophy, and a relative paucity of localizing neurological signs or signs of raised intracranial pressure. Radiographic calcification in muscles was not seen. A CT scan of the brain showed numerous small discrete lesions. Their attenuation density values were appreciably less than that of calcium and they enhanced slightly with contrast. Magnification revealed that these were scolices within cysticerci. There was no enhancement of the cyst wall and no pericystic oedema. CT scan of muscles showed similar cysticerci producing a 'honeycomb' appearance. This is the first CT demonstration of widely disseminated living cysticerci in brain and muscles. It was confirmed histologically. In the absence of palpable cysticerci, the clinical diagnosis can be missed, although no other disease in its full form presents in this manner. The symptoms are mainly caused by the space-occupying effect of the large number of cysticerci rather than by adjacent tissue swelling such as is seen in the presence of dying parasites. Praziquantel was ineffective and hazardous, causing some known and some previously unreported responses and reactions. All 3 patients died.

## INTRODUCTION

There is a voluminous literature on cysticercosis. The main reason to add to this is to present further observations on the use of CT scanning to demonstrate the presence of parasites and on treatment with praziquantel. This is based on 3 similar cases with the disseminated form of the disease observed during the course of a year.

## MATERIAL AND METHODS

The management of 3 patients with disseminated cysticercosis, together with serial CT scans of brain and muscle, biopsy of muscle and subcutaneous nodules and a full autopsy of Case 3 form the basis of this study.

All patients were scanned with a Siemens CT/SDR 3 scanner with scanning time of 5 s. Head CT scans were obtained with 8 mm contiguous sections before and after a bolus intravenous

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injection of 80 ml of Conray 420. CT scans of muscles were obtained with 8 mm noncontiguous sections. Image magnification by a factor of 5 was obtained for finer analysis. The size and attenuation density value of the lesions were obtained by averaging 100 of such images with an electronic cursor. The number of lesions per cm$^2$ was calculated for brain and muscle.

## CASE REPORTS

### *Case 1*

In June 1984, A.N., a male aged 23 yrs, noticed difficulty in expressing himself. A month later, he began having generalized seizures, not controlled with anticonvulsants. After 6 months, symptoms of progressive dementia developed. He complained of painful enlargement of his lower limbs.

In March 1985, examination revealed a mild expressive aphasia, severe memory loss especially for recent events, intellectual deterioration, irrational behaviour and ideas of persecution. There was considerable smooth generalized hypertrophy of the forearms, calves (fig. 1A) and thighs with slight difficulty in rising from a sitting position. The calves measured 39.5 cm in girth. The optic fundi and remainder of the neurological examination were normal. A firm subcutaneous nodule was palpated over the right temple.

Three stool examinations showed no ova. The EEG, ECG, EMG and the serum CK were normal. There was a slight increase in CSF protein content. Skull and soft tissue radiographs showed no abnormal calcification.

CT scan of the brain in March 1985, showed very numerous, small (2–4 mm) high attenuation lesions which at first suggested calcification, but their attenuation values were lower, ranging from 40 to 46 Hounsfield units (mean 43.5 HU). After contrast administration there was slight enhancement (mean 54.2 HU). They numbered 3.5 cm$^2$ of brain (Table 1) and were more numerous in the

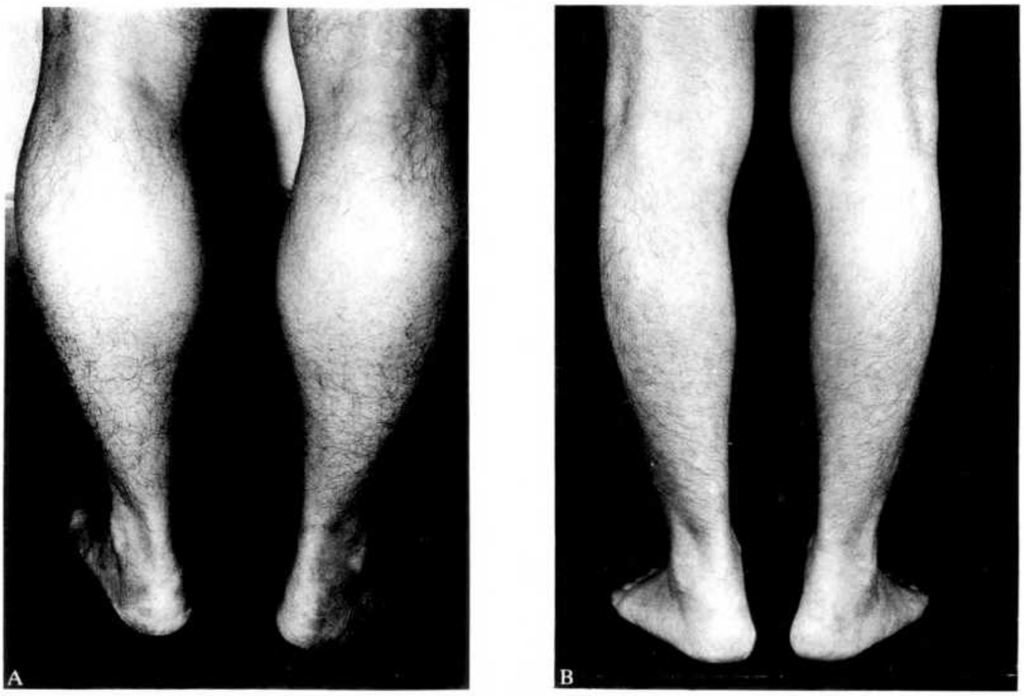

FIG. 1. *Case 1*. A, massive enlargement of calves. B, reduction in size after praziquantel.

cerebrum than in the cerebellum. Magnification showed that most of these lesions were within cysts measuring on an average 8.2 HU. After contrast there was no enhancement of the cyst or of the pericystic region. It was concluded that these were cysticerci, the hyperdense lesions being the scolices. A few cysts without the high attenuation area were also seen in the brain parenchyma, the fourth ventricle and in the right frontal horn. There was no cerebral oedema. The ventricles and basal cisterns were normal.

CT scanning of the muscles of the thighs and calves also revealed a vast number (density 4/cm$^2$) of similar but larger cysts (fig. 2A) measuring 5–7 mm with mean attenuation value of 11 HU in the cystic part and 22 HU in the hyperdense part which was projecting at one pole in most of them (Table 2). There was slight enhancement after contrast of the scolex (25–39 HU), but not of the cyst (9–14 HU). No calcification was seen.

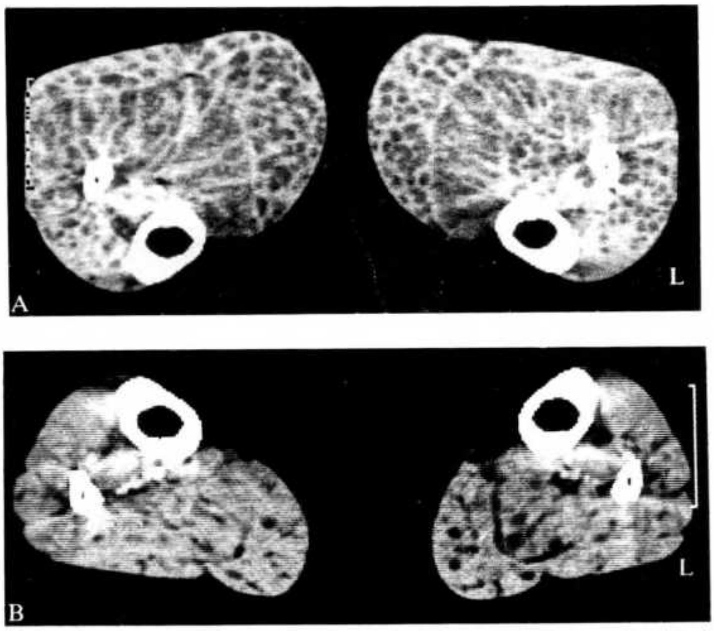

FIG. 2. *Case 1.* A, unenhanced CT scan corresponding to fig. 1A showing honeycomb effect due to innumerable cysts of cysticerci. The scolices are not well visualized and there is no calcification. B, reduction in numbers after praziquantel. Scale in A, B = 5 cm.

At biopsy of an enlarged calf, grape-like bunches of cysticerci extruded into the wound. Histological examination revealed them to have been 'living larvae of Cysticercus cellulosae' without calcification. There was no evidence of polymyositis.

A few days later the patient's condition deteriorated and a 15-day course of praziquantel (PZQ) 50/mg/kg body weight in 3 divided doses was started on March 31, 1985, after 3 days of intravenous mannitol, but without cover with corticosteroid. After the first dose, he complained of headache, vomited and became restless and aggressive. After the third dose, he became unconscious with bilateral dilated and slowly reacting pupils, double incontinence, extensor thrusting and extensor plantar responses. PZQ was stopped and intravenous dexamethasone and mannitol were given. A CT scan showed small ventricles and effacement of the cortical sulci. Only a few of the hyperdense spots were visible, probably because of cerebral oedema. A.N. remained unconscious for 3 days with a high fever and hiccups. On the fifth day he had a bout of acute dyspnoea. By April 10 he had recovered, but his expressive aphasia was more obvious. The EEG showed absence of normal cortical activity and a low voltage generalized theta rhythm with superimposed episodes of 2 Hz generalized high voltage activity.

As PZQ was considered life-saving, a small dose of 200 mg thrice daily was started on April 16 together with intravenous dexamethasone. Two days later generalized urticaria and severe itching appeared. The patient's behaviour deteriorated and there was further painful enlargement of the muscles. However, by April 21, the rash disappeared and his behaviour improved. The dose was gradually raised to 900 mg thrice daily by April 25 and continued until May 7. His muscles became softer and the circumference of the calves diminished to 34.5 cm. (fig. 1B). The nodule in the scalp disappeared and there was also an overall improvement in higher mental function. Anticonvulsants and oral steroids were continued.

In July a CT scan showed normal ventricles, a lesser number of lesions as compared with the first scan and no cerebral oedema. Similarly, there was a remarkable reduction in the number of cysts seen in the CT scan of his muscles (fig. 2B). He remained well until October 1985, when his condition worsened and he died in status epilepticus before he could come to Bombay for a second course of PZQ.

### *Case 2*

From the age of 11 yrs, M.S., a girl aged 17 yrs, had had increasingly frequent focal and generalized seizures and over the 4 to 5 yrs before presentation, progressive mental deterioration had developed. For 2 yrs recurrent crops of subcutaneous swellings had appeared and disappeared all over the body. Her mother had noticed painless enlargement of muscles, especially of the legs.

Examination revealed a large number of nodules all over the body and tongue. There was profound loss of memory, intellect, orientation and other higher mental functions. The optic fundi and the remainder of the neurological examination were normal. Smooth symmetric enlargement of all limb muscles, especially of the legs, was present and she had slight difficulty in rising from a sitting position. She was small, but the circumference of her calves was 36.2 cm.

The routine laboratory tests, CSF, serum CK and EMG were normal. No ova of Taenia solium were found in the stools. The EEG showed bilateral 2-5 Hz slow activity in the frontal regions with focal sharp wave discharges. Inverted T waves were reported in standard lead I and all chest (V) leads of the ECG. No abnormal calcification was seen on plain radiography of the muscles and skull. CT scans of the brain and of limb, neck and chest muscles (figs 3, 4) were similar to those of Case 1. The various measurements are given in Tables 1 and 2. No calcification was seen in brain or muscles and there was no ventricular dilatation or cerebral oedema.

Numerous living cysticerci were found on biopsy of a calf muscle and also from the tongue and a subcutaneous nodule. There was no polymyositis, although mild chronic pericystic inflammatory changes were seen.

After 3 months of oral prednisolone at a dosage of 30 mg daily and carbamazepine, the convulsions lessened and she was mentally more alert. Praziquantel (50 mg/kg) in 3 divided doses per day was then administered. After the third dose when she had received only 2.5 g, she complained of discomfort in the chest, became restless and had generalized seizures. She rapidly became unconscious, her blood pressure fell and she had a cardiorespiratory arrest. She was resuscitated, but her blood pressure could not be maintained and she died 12 h later.

### *Case 3*

R.H., a boy aged 9 yrs, had a bout of fever in November 1984, followed by mental deterioration and apathy. A poor resolution CT scan of the brain and CSF examination were reported normal. Benign intracranial hypertension was diagnosed and he temporarily improved with dexamethasone. In April 1985, he had visual hallucinations and seizures after which marked mental deterioration set in and he became bedridden and incontinent. With dexamethasone, he improved marginally by July, when his mother noticed bilateral proptosis. Our first examination in October revealed a small

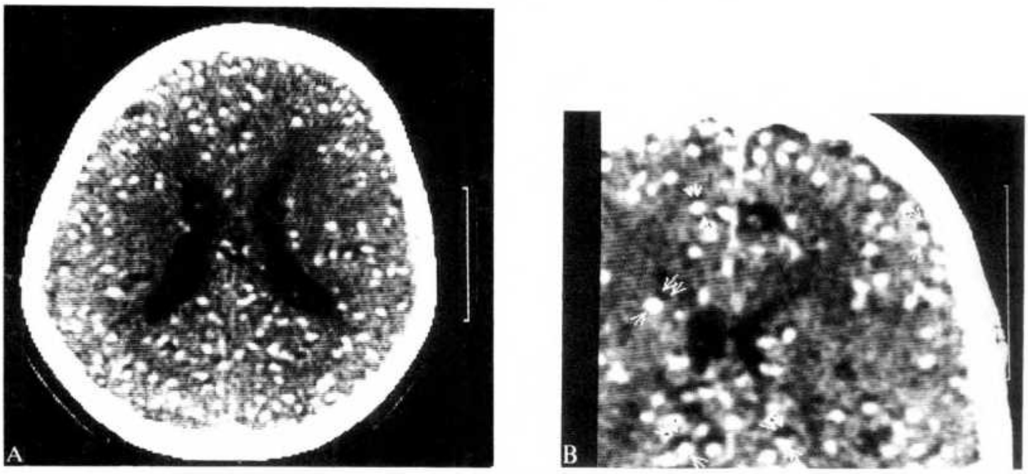

FIG. 3. *Case 2*. A, unenhanced CT scan of brain illustrating the 'sky on a starry night' effect. The small cystic component of the parasites is not well visualized. B, magnified image emphasizing the cysts (double arrow) and the scolices (single arrow). Scale in A, B = 5 cm.

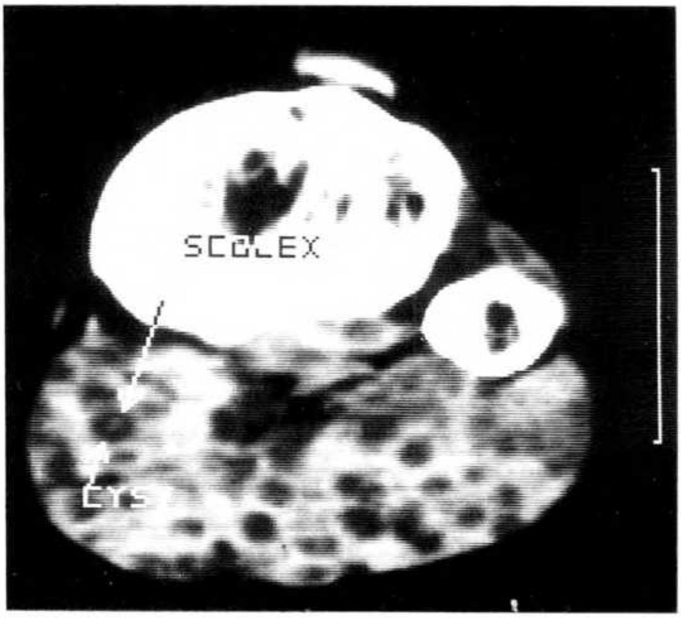

FIG. 4. *Case 2*. Magnified view of unenhanced CT scan of the calf clearly showing cysts with scolices in some of them. Scale = 5 cm.

boy with a moon face, generalized oedema and bilateral proptosis. The fundi were normal, but his pupils were dilated and reacted slowly to light. He was grossly demented and incontinent. There was no obvious paralysis, but detailed muscle testing was not possible. Bilateral grasp reflexes and extensor plantar responses were found. Subcutaneous nodules could not be palpated. A clinical diagnosis of subacute encephalitis or leucoencephalopathy was made.

The EEG showed epileptogenic activity, and the EMG was suggestive of inflammatory muscle disease. Radiological examination revealed separation of the skull sutures, but no calcification in the brain or muscles. The plain, magnified and postcontrast CT scans of the brain were the same as in Cases 1 and 2 (Table 1, and fig. 5A) except that the ventricles were slightly enlarged and there was suture diastasis. A few cysts were seen in the orbits.

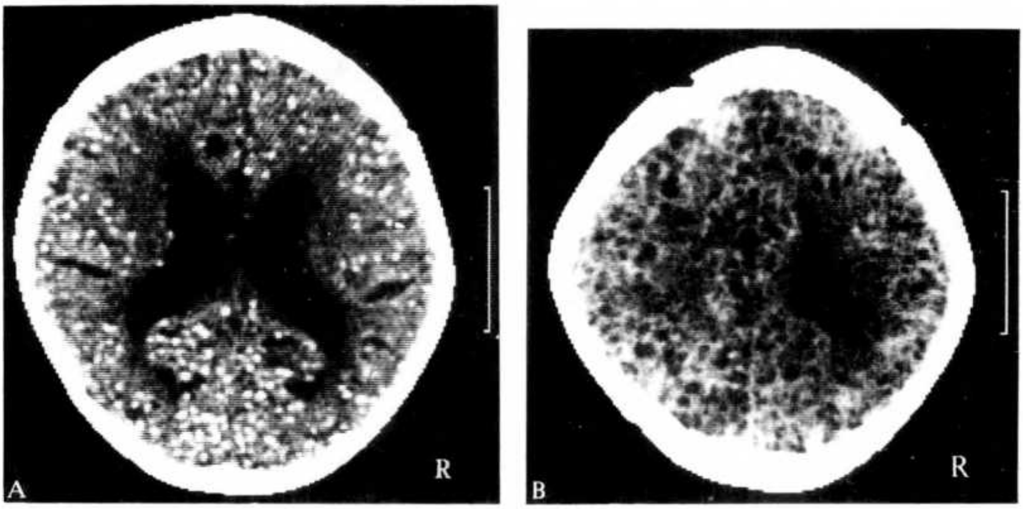

FIG. 5. *Case 3*. A, unenhanced CT scan of the brain showing the 'starry night effect' of scolices. The cysti are not well visualized and there is no calcification. B, scan after praziquantel therapy. The cysts are larger and stand out clearly while the scolices are less well visualized. Scales = 5 cm.

It was then realized that this boy had disseminated cysticercosis with muscle pseudohypertrophy masked by the effects of dexamethasone, the calves measuring 36.2 cm. His mother admitted noticing muscular enlargement even before the administration of dexamethasone. CT scan of limb muscles confirmed this by revealing a large number (4.2/cm$^2$) of cysts (mean 4.5 HU) varying from 3–4 mm in size. Most of these had eccentric areas of high attenuation (42–44 HU) comparable with those in the brain (fig. 6, Table 2). No calcification was seen. The limb muscles were atrophic and smaller in size. There was appreciable increase in subcutaneous fat. During muscle biopsy from the thigh a large number of cysticerci emerged. The histology showed cysticerci with well-defined morphology with a cyst wall, suckers and hooklets. Minimal pericystic and perivascular chronic inflammatory changes were seen. There was no polymyositis.

A prophylactic suboccipital decompression was carried out and on December 31, PZQ was begun with a small dose of only 1.5 mg/kg thrice daily under cover of i.v. dexamethasone. After only 750 mg were administered, he became drowsy, his suboccipital decompression bulged considerably and he had to be ventilated after tracheostomy. A CT scan of the brain on January 8, 1986, did not reveal any significant change. After a 10-day drug holiday during which intravenous mannitol and dexamethasone were given and CSF repeatedly aspirated, PZQ was again started. A smaller dose of 50 mg/day was given for some days and gradually increased to the full dose of 1800 mg/day according to his body weight. This dose was then continued for 20 days. Initially further seizures occurred, and the limb muscles became so swollen that cyanosis of the feet and legs bordering on gangrene appeared and the skin became shiny and tight. Proptosis and chemosis increased menacingly and large vesicular bullae appeared on the hands and legs (fig. 7). Marked systemic hypertension

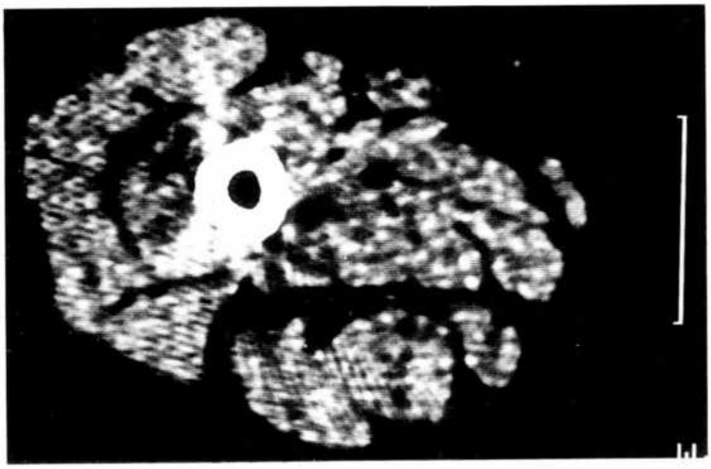

FIG. 6. *Case 3.* Unenhanced CT scan of muscle illustrating clearer visualization of the scolices as hyperdense spots, similar to those seen in the brain. Note muscle atrophy. Scale = 5 cm.

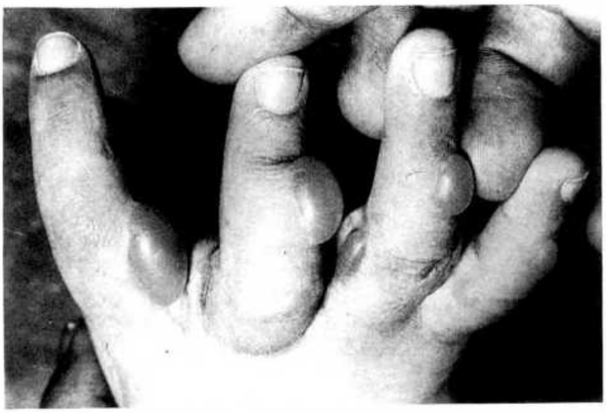

FIG. 7. *Case 3.* Large vesicular bullae on hand during praziquantel therapy.

also developed, requiring antihypertensive drugs. Despite this, treatment with PZQ was persevered with as it was considered life-saving. Later, the swelling and cyanosis of his legs became less and the muscles softer and smaller, although there was no improvement in mental function. A CT scan (February 18) of the brain showed considerable changes (fig. 5B). The cysts were larger in size (5–7 mm). The high attenuation nubbins were relatively less well seen, their attenuation density values having dropped from 20 to 42 HU (precontrast) and 32 to 58 HU after contrast, but there was no change in the values of the cysts. R. H. died 6 weeks later after cardiorespiratory arrest.

The autopsied brain closely resembled the CT scans. The meninges were congested. The brain was studded with cysts, 5–7 mm in diameter, with a density of 5/cm$^2$ (fig. 8). Cysts were seen adherent to the endocardium of the right ventricle and in the pleural cavities. Histological examination confirmed that parasites were viable and no significant calcification was found even in the very scanty dead ones. In the brain there was only a mild local chronic inflammatory reaction, without oedema or neuronal changes.

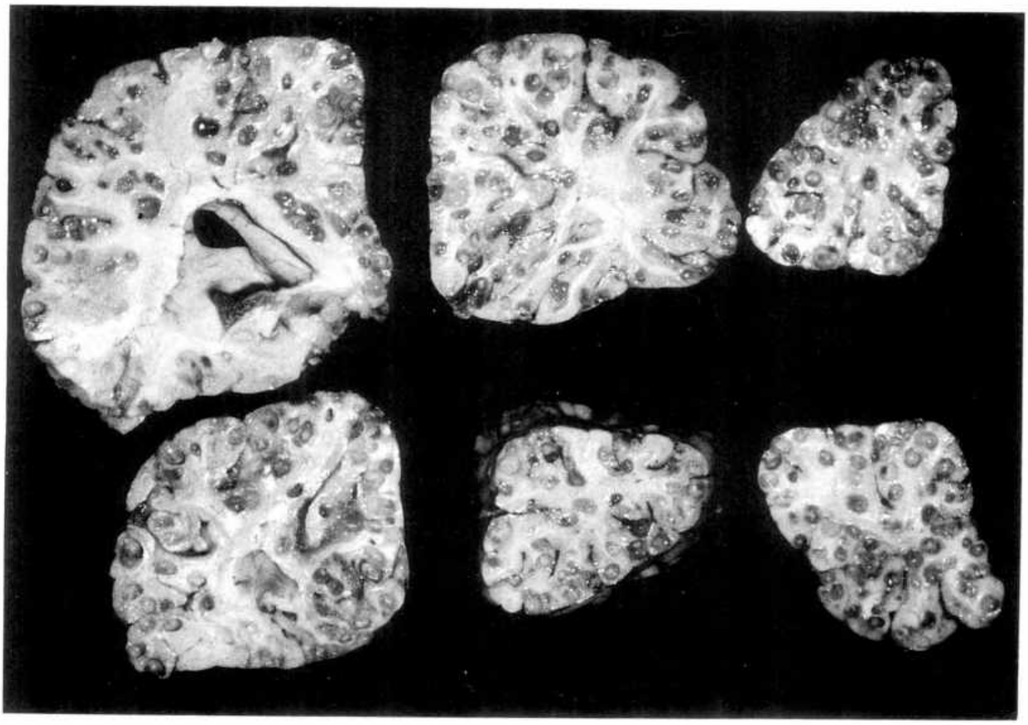

FIG. 8. *Case 3*. Serial sections of brain studded with living cysticercii (5/cm$^2$). Note the close resemblance to the CT scan in fig. 5A.

## RESULTS AND ANALYSIS

### *Clinical*

Table 3 summarizes the information about the 3 patients. All were young. The epileptic attacks were both focal and generalized and difficult to control. The dementia was progressive and disabling. Visual and sensory hallucinations, aggression and paranoia were common early complaints. Case 3 became comatose. Progressive, uniform, and at times painful, enlargement of the calves was followed by enlargement of other muscles, particularly those of the pelvic and shoulder girdles and the masseters.

In none of the patients was muscle weakness remarkable. Headaches were mild, there was no vomiting, and although papilloedema was reported earlier in Case 3, we could not confirm it. Case 1 had mild expressive aphasia and Case 3 had poorly reacting pupils and extensor plantar responses in the later part of the illness. Whereas in Case 1, only one nodule could be palpated under the scalp, in Case 2, nodules appeared and disappeared in crops. None was reported in Case 3 early in the disease, nor could we find any, although they were possibly masked by steroid therapy. However, every time an incision was made in his body, cysticerci appeared.

TABLE 1 SIZE AND ATTENUATION VALUES OF 100 CYSTICERCI VISUALIZED ON CT OF BRAIN AND THEIR FREQUENCY

| Case | *Scolex* | | | *Cyst* | | | *No. of lesions* ($cm^2$) |
|---|---|---|---|---|---|---|---|
| | *Size (mm) (mean)* | *Attenuation (HU) (mean)* | | *Size (mm) (mean)* | *Attenuation (HU) mean* | | |
| | | *Precontrast* | *Postcontrast* | | *Precontrast* | *Postcontrast* | |
| | 2-4 | 40-46 | 46-62 | 1-4 | 7-9 | 7-9 | |
| 1 | (3.1) | (43.5) | (54.2) | (2) | (8.2) | (8.2) | 3.5 |
| | 3-4 | 42-55 | 41-85 | 1-3 | 0-5 | 0-5 | |
| 2 | (3.5) | (48) | (68) | (1.1) | (3) | (3) | 3.5 |
| | 1-2 | 23-59 | 48-68 | 2-3 | 0-12 | 0-12 | |
| 3 | (1.5) | (44.7) | (58) | (2.3) | (4.2) | (4.2) | 4.1 |

TABLE 2 SIZE AND ATTENUATION VALUES OF 100 CYSTICERCI VISUALIZED ON CT OF MUSCLES AND THEIR FREQUENCY

| Case | *Scolex* | | *Cyst* | | *No. of lesions* ($cm^2$) |
|---|---|---|---|---|---|
| | *Size (mm) (mean)* | *Attenuation (HU) (mean)* *Precontrast* | *Size (mm) (mean)* | *Attenuation (HU) (mean)* *Precontrast* | |
| | 1-3 | 18-26 | 5-7 | 5-20 | |
| 1 | (2) | (22) | (5.2) | (11) | 4 |
| | 2-3 | 19-20 | 5-6 | −2-20 | |
| 2 | (2.8) | (19.5) | (5.4) | (6.9) | 4 |
| | 1-2 | 42-44 | 3-4 | −3-11 | |
| 3 | (1.6) | (43) | (3.1) | (4.5) | 4.2 |

Postcontrast enhancement of scolices (25-39 HU) but not of cysts (9-14 HU) was observed in Case 1

## *Radiology*

Plain x-rays did not reveal calcification in the brain or muscles. The striking appearance in the unenhanced CT scan of the brain was due to countless small discrete areas of high attenuation (figs 3A, 5A) in every cut. We likened it to the 'sky on a starry cloudless night' as the similarity was dramatically apt. On initial visual assessment, these appeared to us to be calcifying lesions, but the attenuation density values of a hundred such in each patient were clearly less than that of calcium (Table 1). Some enhancement of these lesions was seen after injection of contrast. On magnification, more details were appreciated. The majority of these lesions were seen to lie within a small nonenhancing cyst. There was no ring enhancement after contrast (fig. 3B). We realized that we were seeing the scolex and cyst of intact cysticerci. There were 3.5 to 4.1/$cm^2$ area of brain, indicating their vast number. Depending on the plane of the cut, a few cysts without the high attenuation areas were also seen. The ventricles were normal in size except in Case 3 in whom they became dilated later in the disease.

CT scans of muscles revealed a large number of cystic lesions (figs 2A, 4). Most

TABLE 3 DATA FOR 22 PATIENTS WITH DISSEMINATED CYSTICERCOSIS

| No. | *Name of first author* | *Place and year of report* | *Age at onset (yrs)/sex* | *Duration of illness on admission (months)* | *Seizures* | *Mental and behavioural disorder* | *Pseudo-hypertrophy of muscles* | *Raised intra-cranial tension* | *Focal neuro-logical deficit* | *Palpable subcuta-neous nodule* | *Biopsied cysticerci in muscles* | *X-ray soft tissue calcifi-cation* | *CT scan cysticerci in brain/muscles* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Literature review | | | | | | | | | | | | | |
| 1. | Priest | India 1926 | 24/M | 1 | + | + | + | NA | — | + | + | NA | NA |
| 2. | McRobert | India 1944 | 24/M | 6 | + | — | + | — | — | + | NA | — | NA |
| 3. | McGill | India 1948 | 25/M | 4 | + | + | + | — | + | + | + | — | NA |
| 4. | McGill | India 1948 | 19/M | 12 | — | — | + | — | — | + | + | — | NA |
| 5. | Singh | India 1957 | 22/F | 30 | + | + | + | — | — | + | + | — | NA |
| 6. | Prakash | India 1965 | 13/M | 11 | + | + | + | — | — | + | + | — | NA |
| 7. | Jacob | India 1968 | 20/M | 36 | + | + | + | — | — | + | + | — | NA |
| 8. | Armbrust-Figueiredo | Brazil 1970 | 34/F | 8 | + | — | + | — | — | — | + | — | NA |
| 9. | Jolly | India 1971 | 21/M | 8 | + | — | + | — | — | + | + | — | NA |
| 10. | Jolly | India 1971 | 23/M | 18 | — | + | + | — | — | + | + | — | NA |
| 11. | Rao | India 1972 | 9/M | 6 | — | — | + | — | — | + | + | — | NA |
| 12. | Salgaokar | India 1972 | 11/M | 1 | — | + | + | — | — | + | + | — | NA |
| 13. | Vigg | India 1975 | 43/F | 24 | + | + | + | — | + | + | + | + | NA |
| 14. | Vigg | India 1975 | 34/F | 12 | + | — | + | — | — | + | + | NA | NA |
| 15. | Sawhney | India 1976 | 23/F | 8 | + | + | + | — | — | + | + | NA | NA |
| 16. | Vijayan | India 1977 | NA/M | NA | + | — | + | + | — | + | + | — | NA |
| 17. | Zhu | China 1983 | 39/M | 16 | + | — | + | — | — | + | NA | NA | NA |
| 18. | Zhu | China 1983 | 23/M | 18 | + | + | + | + | — | + | NA | NA | NA |
| 19. | Zhu | China 1983 | 30/F | 48 | + | + | + | — | — | + | + | NA | NA |
| Present cases | | | | | | | | | | | | | |
| 20. | Wadia | India 1987 | 22/M | 12 | + | + | + | — | + | + | + | — | +/+ |
| 21. | Wadia | India 1987 | 11/F | 72 | + | + | + | — | — | + | + | — | +/+ |
| 22. | Wadia | India 1987 | 8/M | 12 | + | + | + | + | — | — | + | — | +/+ |
| | Total | | | | 18 | 14 | 22 | 3 | 3 | 20 | 19 | 1 | 3/3 |

+ = present — = absent NA = not available/not done.

of them showed well-defined homogeneous high attenuation density nubbins (scolices) projecting inside the cyst. Their values were clearly greater in Case 3 (Table 2), reaching the ranges seen in the brain and making them visually more obvious (fig. 6) than in the other 2 cases in whom magnification was required. No calcification was seen in the brain or muscles.

### *Neurophysiology*

Electromyography was normal in Cases 1 and 2, but showed some evidence of inflammatory muscle disease in Case 3. Electroencephalography showed non-specific changes reflecting the generalized cerebral disorder with bilateral slow and focal sharp waves.

### *Praziquantel (PZQ) therapy*

The response and reactions to PZQ can best be divided into two groups: (1) related to the tissue where cysticerci were lodged, namely the brain, muscles and orbits; and (2) general reactions.

1. *Reactions in tissues containing parasites: intracranial reactions.* There was rapid deterioration in the level of consciousness in all 3 patients when PZQ was initially administered. Case 1 who had, in addition, dilated poorly-reacting pupils, extensor spasms, extensors plantar responses and cerebral swelling as judged by the CT scan, was barely salvaged by large doses of dexamethasone and mannitol. Despite priming with dexamethasone, Case 2 had generalized convulsions, irreversible hypotension and died from cardiorespiratory arrest within a day of commencement of therapy. Case 3 became restless, went into deeper coma and required assisted ventilation.

The dosage required to cause these severe reactions was small. The effect was evident by the second standard dose of 50 mg/kg body weight in the first 2 patients, and only a tenth of that dose in the third patient. Previous priming with steroids and mannitol and even suboccipital decompression did not seem to blunt the effect of the reaction.

As PZQ was considered to be life-saving, a second attempt was made to administer it to the 2 surviving patients after a drug-free interval. Although the dosage was slowly built up (under cover of dexamethazone), mild cerebral disturbances were observed during the first few days. However, this did not prevent us from completing the full course of PZQ (50 mg/kg/day for 15–20 days).

Some beneficial effect of PZQ was seen in the first patient as his higher mental functions improved and the CT scan showed regression of the brain swelling and an appreciable reduction in the number of cerebral lesions. The third patient, whose treatment began at an advanced stage, derived no perceptible benefit. The CT scan after PZQ showed an increase in the size of cysts, but at autopsy the cysticerci were still viable.

*Reaction in muscle.* In the 2 surviving patients, even with a smaller initial dose at the second attempt, there was a remarkable painful increase in the size and tension of the enlarged muscles, leading to vascular obstruction bordering on gangrene in Case 3. At the end of the course, however, his muscles became soft and there was a measurable reduction in their size (fig. 1B).

The CT scan of the muscles in Case 1 showed a corresponding reduction in the number of cysts (fig. 2B). Case 3 was too ill for the CT scan to be repeated.

*Intraorbital reaction.* In Case 3, the chemosis and proptosis increased dangerously, leading to near dislocation of the globe of the left eye.

2. *General reactions.* The case histories record fever, hiccups, severe itching, generalized urticarial rash, large multiple cutaneous bullae (fig. 7) over the hands and feet, and a significant rise of blood pressure in the 2 patients who completed their treatment. A short acute bout of dyspnoea after the first aborted course of PZQ in Case 1 also deserves mention.

In the final analysis PZQ was ineffective as all 3 patients died.

### *Biopsy and autopsy examination*

The histological examination of the cysticerci from biopsied muscles, tongue and subcutaneous nodules, and autopsied brain and heart (even after a full course of PZQ) showed mostly living cysticerci. No detectable calcification was seen even in the few dead organisms. Both in the brain and muscles no significant oedema or inflammatory reaction was evident.

## DISCUSSION

Although widespread dissemination of cysticerci throughout the human body was reported by Krishnaswami from Burma as early as 1912 and by British Army medical officers stationed in India (Priest, 1926; McRobert, 1944; McGill, 1948), more recent disease classifications (Grisolia and Wiederholt, 1982; Groll, 1982; Sotelo *et al.*, 1985*a*; Estañol *et al.*, 1986; Vasconcelos *et al.*, 1987) have failed to lay stress on this form of clinical presentation, perhaps because of its relative rarity. The patient reported by Krishnaswami (1912) had muscle pains, easy fatigue and clinically palpable cysticerci; dissemination was shown in muscles and various organs at postmortem. Priest (1926) described 'a case of extensive somatic dissemination of cysticercus cellulosae in man' in a British soldier, who had corresponding physical signs of 'Sandow' type: swelling of muscles, epileptic seizures, mental dullness and widespread subcutaneous nodules. Extensive invasion of a deltoid muscle by cysticerci was found when muscle biopsy was performed. His patient did not have symptoms of raised intracranial pressure. Calcified cysticerci were not seen radiologically in the brain or muscles. When describing a similar case of a man who in a matter of 6 months had come to resemble 'a professional wrestler to the amusement of his friends and dismay of his household', McRobert (1944) stressed the absence of calcification in the muscles on extensive radiological examination. McGill (1948) makes the point that a vast number of living cysticerci are disseminated throughout the body. Yet it is interesting that

Dixon and Hargreaves (1944) and Dixon and Lipscomb (1961) in their landmark papers reporting their collection of 450 cases of cysticercosis in the British Army in India during the same era, mention only one such case which had already been reported earlier by Priest (1926).

Since then, as shown in Table 3, a number of similar cases have been published (Priest, 1926; McRobert, 1944; McGill, 1948; Singh and Jolly, 1957; Prakash and Kumar, 1965; Jacob and Mathew, 1968; Armbrust-Figueiredo *et al.*, 1970; Jolly and Pallis, 1971; Rao *et al.*, 1972; Salgaokar and Watcha, 1972; Vigg and Rai, 1975; Sawhney *et al.*, 1976; Vijayan *et al.*, 1977; Zhu and Xu, 1983), although more discussion has been devoted to the pseudohypertrophy of muscles in most of them rather than on the massive dissemination of which it forms a part. It is interesting that from the available literature, 15 cases (excluding ours) were from India, 3 from China and 1 only from South America (Brazil) where cysticercosis is rampant. Zhu and Xu (1983), however, mention 10 other cases of muscular pseudohypertrophy reported in China, which were not accessible for our study.

Table 3 shows that the majority of patients were young and there were more males than females. Our own experience and that of others shows that intractable epilepsy, dementia, enlargement of muscles, relative absence of focal neurological signs or obviously raised intracranial pressure, at least until late in the disease, and subcutaneous and lingual nodules, are the main features of disseminated cysticercosis. Absence of calcification in soft tissues and the head on radiological examination and the presence of living cysticerci at biopsy or autopsy are important findings, although the latter has not been sufficiently stressed. It is pertinent to point out that appreciable enlargement of muscles can only occur when they are invaded by a large number of living cysticerci and that this happens when there is massive, though at times subclinical, dissemination all over the body including the brain.

This paper adds a new dimension in diagnosis by showing specific changes in the CT scan of the brain and muscles. We have demonstrated that it is possible to show not only the morphology of the cysticerci, but their vast numbers and dissemination throughout the body. In the unenhanced CT scan of the brain, the innumerable high attenuation spots gave the initial mistaken impression on superficial inspection of calcifying cysticerci to which one of us made a passing reference (Wadia, 1987).

By using appropriate magnification, thin section study and carefully measuring the attenuation values of a hundred such hyperdense spots, we realized that these actually represented scolices with an attenuation value significantly less than that of calcium. We also realized that their large numbers and striking appearance masked the small cysts, mostly with a density equivalent to that of CSF, within which most of them (depending on the cut) were seen to be lying. What was being observed was a large number of viable cysticerci, and not calcified, dying or dead parasites. The enhancement, although slight, of the high density spots after contrast administration, the absence of enhancement of the cyst wall, and the negligible surrounding cerebral oedema, together with the absence of calcification even in the scolex, further strengthened this conclusion. Confirmation came later when the autopsied brain of Case 3 showed mostly living cysticerci. Whereas a variety of CT scan observations have been made on neurocysticercosis, there is no earlier report comparable to ours, especially of the unenhanced CT scan. This is surprising, as pathological specimens of the brain studded with cysticerci not uncommonly illustrate accounts of this subject. Lee (1983), however, has referred to visualization of the scolex by contrast enhancement in a patient with a single large intraparenchymal cyst. He also stressed the fact that absence of pericystic oedema and enhancement after contrast administration were signs of a living cysticercus larva in the brain. Vasconcelos *et al.* (1987) mentioned small disseminated hyperdense spots only seen after contrast administration in 'miliary cysticercosis', but they did not state whether these represented the scolex or the whole cysticercus, although the impression given on the basis of 2 biopsied lesions was that they were involuting cysticerci.

The unenhanced CT scan examination of the muscles of our patients is unique and it has been briefly referred to earlier (Wadia, 1987). The innumerable cysts stood out clearly against the background of the muscle mass in which they were embedded, the CT image appearing like a honeycomb, or leopard spots. The scolices were less well visualized, especially in our first 2 patients and better identified on magnification. The absence of calcification suggested living cysticerci, an observation later confirmed histologically.

It is noteworthy that the CT images are somewhat different in the brain and muscle although scanned at the same time. Besides the age and viability of the cysticerci (which we concluded from the biopsies and autopsy were more or less the same in brain and muscle), the CT image effect depends on the size and attenuation values of the scolex and cyst, and the morphology and attenuation values of the background tissue. In the brain, the 'starry night effect' is produced by the scolices which stand out sharply as hyperdense spots against the brain which has a lower attenuation value. The cysts contribute little to the image, as they are smaller in size than in muscle. On the other hand, the cysticerci are more loosely packed in muscle and the relatively larger cysts appear prominently against the muscle mass of much higher density value, giving the honeycomb appearance. The scolices are less well visualized as they are of lesser attenuation value than in the brain except in our Case 3 where they add a slight speckling effect within the cysts, but not as striking as in the brain.

Epilepsy and progressive dementia are well-known symptoms of various forms of cysticercosis and also of several other diseases of children and adults. Similarly, isolated enlargement of muscles raises several diagnostic possibilities. Yet seizures, progressive dementia and enlargement of muscles encountered together are seen in no other human disease apart from disseminated cysticercosis. The detection of palpable cysticerci makes the diagnosis easier. In such a case, CT scan findings merely add one more dimension to the diagnosis, but are still invaluable by confirming the not always appreciated massive dissemination, which indicates a relatively bad prognosis and requires great care in planning therapy.

The value of the CT scan becomes clearly greater in those patients in whom all the clinical features have not appeared. For example, the first described patient of the disseminated type by Krishnaswami (1912) had only painful, but not enlarged muscles, yet autopsy revealed widespread dissemination of cysticerci and a brain studded with them. Similarly, Table 3 shows that 2 (4, 11) of the 22 patients presented with only pseudohypertrophy of muscles. Cysticercosis would have been diagnosed by the distinctive CT scan images of the muscles even without biopsy and silent dissemination shown by CT of the brain. Our third patient is another case in point. He presented with seizures and dementia and an initial clinical diagnosis of subacute encephalitis or leucoencephalopathy was made. It was the CT scan of the brain which was pathognomonic and led us to scan his muscles which showed the classical images of the disease. The muscle biopsy merely followed in confirmation.

CT scan of the brain showing multiple hyperdense lesions, taken in isolation, raises its own questions regarding differential diagnosis, especially in the setting of a tropical country. Such lesions are seen in other forms of cysticercosis, tuberculoma, toxoplasmosis, cytomegalovirus inclusion disease, congenital viral encephalitis, paragonimiasis, Toxocara canis infection, secondary deposits and tuberous sclerosis. Each has its clear differentiating points, calcification being the striking feature in many of them (Lee, 1983; Bonstelle, 1985; Williams, 1985). Planned CT examination clears the differential diagnosis by showing cysts with a demonstrable scolex in most of them, the absence of calcification and the vast numbers.

The classical honeycomb appearance of disseminated cysticercosis has no alternative diagnosis and it is somewhat surprising that muscle scanning has not been used before in the diagnosis of cysticercosis generally. The radiological demonstration of calcification in dying and dead cysticerci in muscle is a well established pathognomonic sign of cysticercosis and we have used the finer CT scan examination in several other patients to highlight the calcification when the plain radiology has not shown it well or has failed to reveal it. Similarly, it may be possible to demonstrate cysts in the muscles of some patients with cysticercosis as the only supportive evidence of neurocysticercosis, especially when a nodule is not available for biopsy.

No clear evidence of myositis was found in our patients, this perhaps helping to settle a controversy (Singh and Jolly, 1957; Prakash and Kumar, 1965; Jacob and Mathew, 1968; Armbrust-Figueiredo *et al.*, 1970; Jolly and Pallis, 1971; Salgaokar and Watcha, 1972; Vigg and Rai, 1975; Sawhney *et al.*, 1976) as to whether actual inflammation beyond the immediate cyst wall ever occurs.

The new drug praziquantel (PZQ) has accumulated much acclaim in the treatment of cysticercosis and indications and contraindications for its use have been proposed (Groll, 1982; Sotelo *et al.*, 1985*a*, *b*; Estañol *et al.*, 1986; Vasconcelos *et al.*, 1987). In contrast, all our patients reacted sharply to the administration of PZQ. The mechanism of these severe reactions is unclear, but could have resulted from different combinations of (1) enlargement of cysts as seen in the CT scan of Case 3, (2) massive release of antigen, causing local tissue swelling as exemplified by the post-PZQ CT scan of Case 1, and (3) a generalized anaphylactoid reaction. The first and second were clinically expressed as a rapid rise of intracranial pressure, further enlargement of muscles, and proptosis. The third could explain the sudden hypotension and cardiorespiratory collapse in Case 2 and some of the more minor general reactions. These complications were not dose-related and possibly what was important was the total antigenic quantum released by the large number of cysticerci.

Corticosteroids have been effective in the management of patients with neurocysticercosis, but there are divergent views regarding its concomitant use with PZQ (Groll, 1982; Spina-França *et al.*, 1982; DeGhetaldi *et al.*, 1983; Sotelo *et al.*, 1984). Dexamethasone was useful to some extent in the management of our patients, at least in countering the acute reactions. We now suggest that patients with disseminated cysticercosis should be primed with oral dexamethasone which should be continued throughout the full course. Injectable dexamethasone may become necessary. We also advise small initial doses of PZQ and careful monitoring. Longer and repeated courses may be required for satisfactory results as Vasconcelos *et al.* (1987) have recommended for 'very large or highly numerous cysts'.

Clinical examination and CT scans after a full course of PZQ therapy showed that there was some effect of the drug on the parasites in our first patient. A second course might have been more effective. The third patient presented with advanced disease and though there was no improvement in his cerebral symptoms, his muscles shrank in size. There was also a change in the CT scan image of the brain which showed larger cysts and less hyperdense scolices. We do not know how this change was brought about by PZQ, but it could not have been therapeutically effective as the cysticerci were alive when examined at autopsy. Zhu and Xu (1983) are the only other workers who have used PZQ in similar patients and their experience was more rewarding. After an initial worsening they noticed a reduction in the size of muscles, in the frequency of seizures and in headaches. No major complications were reported. No CT examinations were undertaken to record the actual changes.

In conclusion, in this form of the disease a large number of cysticerci become embedded all over the body and the symptoms are caused by their space-occupying effect, essentially in the brain and muscles, rather than by causing adjacent tissue reaction and swelling. This parenchymatous cysticercosis occupies the opposite end of the spectrum from that in which dead, calcified cysticerci cause no symptoms or only seizures. It is important that clinical and CT scan classifications include it, as it has a relatively poorer prognosis and needs planned therapy. Further, a more refined CT scan examination would help in many ways generally in cysticercosis.

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# STEELE-RICHARDSON-OLSZEWSKI SYNDROME

## BRAIN ENERGY METABOLISM, BLOOD FLOW AND FLUORODOPA UPTAKE MEASURED BY POSITRON EMISSION TOMOGRAPHY

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## SUMMARY

Brain function was measured in 5 patients with clinically diagnosed Steele-Richardson-Olszewski syndrome using positron emission tomography and tracers of dopamine metabolism, blood flow and oxygen metabolism. A global decrease in blood flow and oxygen utilization compared with normal values was found but the decrease was more marked in the frontal regions. The degree of impairment in oxygen utilization in the frontal region paralleled roughly the duration of the disease. Blood flow was impaired to a greater extent than oxygen utilization, resulting in raised oxygen extraction. This can partially be explained by a lower $pCO_2$ in the patients. Alternatively it may imply involvement of brain vasculature in the pathophysiology of the disease in addition to neuronal degeneration. Striatal dopamine formation and storage, as indicated by L-($^{18}$F)fluorodopa uptake, was significantly decreased compared with control values. The severity of this decrease paralleled the degree of reduction in frontal cerebral blood flow. The results suggest that the impairment of cerebral function in Steele-Richardson-Olszewski syndrome is determined to a large extent by brainstem pathology.

## INTRODUCTION

The Steele-Richardson-Olszewski (SRO) syndrome (progressive supranuclear palsy) (Richardson *et al.*, 1963; Steele *et al.*, 1964; Steele, 1972) is characterized clinically by supranuclear ophthalmoplegia, pseudobulbar palsy, dystonia, axial rigidity and dementia. Cerebellar and pyramidal signs and symptoms are minor or absent. The disease usually starts in the sixth decade and progresses inexorably to death after 2 to 12 yrs, with a median duration from onset to death of 5.9 yrs (Maher and Lees, 1986). Neuropathological findings include neurofibrillary tangles and nerve cell loss with gliosis in specific brainstem, diencephalic and cerebellar nuclei. The cerebral cortex seems to be little affected, if at all (Steele *et al.*, 1964; Jellinger *et al.*, 1980). This has led some to designate the dementia associated with the SRO syndrome as a 'subcortical dementia' (Albert *et al.*, 1974; Cummings and

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Benson, 1984; Whitehouse, 1986). D'Antona *et al.* (1985) showed that cortical glucose utilization measured with positron emission tomography (PET) in 6 patients with probable SRO syndrome was clearly impaired, particularly in the prefrontal regions. These authors postulated that the cortical hypometabolism is caused by the direct influence of subcortical systems on the cortex. Another group (Foster *et al.*, 1986) reported, in abstract form, 5 patients with the SRO syndrome studied with PET. Relative values for glucose utilization were measured, which were depressed in the superior frontal regions.

We have also had the opportunity to investigate 5 patients with probable SRO syndrome using PET. Regional cerebral blood flow (CBF), fractional oxygen extraction (OER) and oxygen utilization ($CMRO_2$ = cerebral metabolic rate of oxygen) were measured, providing information on cerebral metabolism and haemodynamics. L-($^{18}$F)fluorodopa uptake into the striatum was used to assess presynaptic striatal dopaminergic function, thus indicating the integrity of the nigrostriatal dopaminergic system. The substantia nigra is one of the brainstem nuclei which is known to be severely involved in the disease (Steele *et al.*, 1964; Jellinger *et al.*, 1980).

The aim of our study was to characterize further both general and specific aspects of brain metabolism in this condition.

## SUBJECTS AND PATIENTS

### *Healthy volunteers*

L-($^{18}$F)fluorodopa uptake was compared with the values obtained in 5 healthy volunteers, scanned according to the same protocol as the patients. This is because the concentration of radionuclide accumulated in tissue depends on the time of measurement after injection of L-($^{18}$F)-fluorodopa (Leenders *et al.*, 1986*b*). The ages ranged from 30 to 64 yrs (mean ±SD 45±14 yrs). No effect of age on tracer uptake was found in this group.

CBF and oxygen metabolism were measured in 5 other healthy volunteers, who were selected for age (mean ±SD 62.4±1.14 yrs). Although the effect of age on brain energy metabolism is not large (Frackowiak *et al.*, 1980), age matching was considered prudent.

### *Patients*

Five patients with a probable SRO syndrome were investigated. In 1 case pathological confirmation of the diagnosis subsequently became available. One patient (Case 5) was studied with the tracer L-($^{18}$F)fluorodopa only. The clinical data are summarized in Table 1. It should be added that none of the patients responded to a therapeutic dose of levodopa which was tried for short periods several months or years before the present investigations.

*Case 1.* A 60-yr-old man at the age of 57 yrs started to experience falls, walking difficulty and speech problems. In addition he had slowed mentally and became emotionally labile. On examination he had a widebased ataxic gait, marked dysarthria, severe supranuclear gaze palsy and dementia. The Webster scale score was 27 (Webster, 1968). His CT brain scan and EEG were normal. Psychological testing at the time of the PET scans yielded a verbal IQ score of 76 and a performance IQ of 70 on the WAIS. He was considered to be moderately demented although memory and perceptual skills could not be assessed fully because of the gaze palsy.

*Case 2.* A 68-yr-old man at the age of 63 yrs started to complain of tiredness, poor balance and falls backwards. Progressive slowness, slurred speech, emotional lability and forgetfulness then appeared, followed by writing and swallowing difficulties. On examination he showed a severe spastic dysarthria with marked verbal perseveration and poverty of expression. Bilateral limb bradykinesia with axial and limb rigidity, vertical gaze palsy and ankle clonus were also present. The Webster score was 24. A CT brain scan showed slightly expanded ventricles. The WAIS yielded a performance IQ of 76 but his verbal IQ was impossible to test because of language difficulties. There was evidence of dysphasia and of marked perceptual impairment.

*Case 3.* A 65-yr-old man developed dysarthria, dysphagia, backward falls and difficulty in turning at the age of 60 yrs. Later, slight forgetfulness and emotional lability were noted. On examination, pseudobulbar palsy, a mild supranuclear gaze palsy, severe tonic inhibition of levator palpebrae (apraxia of eyelid opening) and general slowness of movement were found. His score on the Webster scale was 20. An EEG, CT scan and MRI scan were normal. Psychological testing at the time of the PET scans yielded a verbal IQ of 83 and a performance IQ of 91 (WAIS). His memory skills were weak but his naming and perceptual skills were normal.

*Case 4.* A 65-yr-old man at the age of 59 yrs started to complain of a reduction in the volume of his voice. This was followed by progressive slowness of movement and falls. He also had visual disturbances, swallowing difficulties and some mild forgetfulness. On examination at the time of the PET investigations he had severe dysphonia and dysarthria, complete supranuclear ophthalmoplegia, axial rigidity and bilateral extensor plantar responses. The score on the Webster scale was 30. A CT scan showed no abnormalities except for widening of the anterior part of the interhemispheric fissure. A WAIS examination performed 6 months before the PET scans gave a verbal score of 110 and a performance score of 70. Verbal memory was normal but performance on memory for faces was defective and picture naming was also impaired. The patient died about 6 months after investigation. The clinical diagnosis of SRO syndrome was confirmed at postmortem.

*Case 5.* A 64-yr-old woman had a 3 yr history of walking difficulty, slowness and backward falls. On examination she stared, was emotionally labile and dysphonic. There was a supranuclear downgaze palsy, dystonia and bradykinesia. Her plantar responses were equivocal. The Webster scale score was 24. Her EEG was normal as was a CT scan, although the frontal sulci were wider than the parieto-occipital sulci. Psychological testing (9 months before her L-($^{18}$F)fluorodopa PET scan) yielded a WAIS verbal IQ of 95 and a performance IQ of 96. She was mentally slow and the usual recognition memory tests could not be administered but she performed poorly in an easy picture recognition test. The result of perceptual tests was below normal.

Written informed consent was obtained from the patients and their spouses and from the healthy volunteers. The protocols were approved by the Hammersmith Hospital Ethics Committee and the Administration of Radioactive Substances Advisory Committee of the UK.

## METHODS

### *L-($^{18}$F)fluorodopa*

This compound is an analogue of L-DOPA (Garnett *et al.*, 1978, 1983). Labelling with the positron emitting radionuclide fluorine-18 (physical half life 110 min) was performed according to the method of Firnau *et al.* (1984). A mixture of 2-, 5- and 6-($^{18}$F)fluorodopa was produced (35%, 5% and 60%, respectively). Typically 2–4 mCi radioactivity contained in 8 mg levodopa was injected intravenously; 75 mg carbidopa was given orally 30 min before injection of the tracer to block peripheral decarboxylation. A series of 6 consecutive 10 min PET scans, using the ECAT-II (EG and G Ortec) single slice whole body tomograph (transaxial resolution 17 mm FWHM; slice thickness 16 mm), was started at 120 min after administration The scanning plane was 4 to 5 cm above and parallel to the orbitomeatal line at the level of the bulk of the striatum. Radioactivity in arterial plasma was measured in all subjects from the moment of administration of the tracer until the end of the scan according to a predetermined sequence of samples. After data collection, attenuation correction by measurement and reconstructions using standard tomographic computer procedures were performed enabling the display of the scanned cross-section of the brain as the distributions of activities pixel by pixel in absolute units. Regions of interest (ROI) were defined in the striatal regions and surrounding brain according to a previously described method (Leenders *et al.*, 1986*b*). For each subject or patient, an average ratio of striatal to surrounding cerebral activity was calculated from all measurements between 120 and 180 min after tracer administration.

TABLE 1. CLINICAL DATA OF THE PATIENTS

| | *Age (yrs)* | *Sex* | *Duration of disease (yrs)* | *Clinical disability* | | | *CT* | *WAIS* | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | *Physical* | *Mental* | *Webster* | | *Verbal* | *Performance* |
| Case 1 | 60 | M | 3 | Severe | Moderate | 27 | Normal | 76 | 70 |
| Case 2 | 68 | M | 5 | Severe | Moderate | 24 | Expanded ventricles | — | 76 |
| Case 3 | 65 | M | 5 | Moderate | Mild | 20 | Normal | 83 | 91 |
| Case 4 | 65 | M | 6 | Severe | Moderate | 30 | Widened hemispheric fissures | 110 | 70 |
| Case 5 | 64 | F | 3 | Moderate | Mild | 24 | Widened frontal sulci | 95 | 96 |

Native dopamine and enzymes for dopamine production and break-down are highly concentrated in striatal tissue in the nerve terminals of the nigrostriatal dopaminergic neurons (Hornykiewicz, 1972). Retention of radioactivity in striatum over time after L-($^{18}$F)fluorodopa administration expresses the capacity of the dopaminergic nerve terminals to form and store ($^{18}$F)dopamine (Garnett *et al.*, 1983; Leenders *et al.*, 1986*b*).

### *Regional CBF, cerebral oxygen extraction and oxygen utilization ($CMRO_2$)*

These were measured with the same tomograph on a different day. The steady-state oxygen-15 inhalation technique was used and supplemented by an inhalation of carbon-11 labelled carbon monoxide. The technical and methodological aspects of these techniques have been extensively discussed elsewhere (Jones *et al.*, 1976; Frackowiak *et al.*, 1980; Lammertsma *et al.*, 1981*a*, *b*, 1982; Lammertsma and Jones, 1983). Applications of these methods to patients with movement disorders have also been published previously (Leenders *et al.*, 1985*c*; Wolfson *et al.*, 1985). Two transaxial planes were scanned, the lower at the level of the striatum (between 4 and 5 cm above and parallel to the orbitomeatal line) and the higher plane at the level of the centrum semiovale (6 cm above and parallel to the orbitomeatal line). For both planes, cortical, white matter and basal ganglia ROIs were defined visually from a video display unit (Leenders *et al.*, 1985*a*, *c*; Wolfson *et al.*, 1985).

Head positioning was identical for patients and healthy volunteers. Although the patients had some nuchal rigidity, no abnormal twisting was observed. The mild to moderate rigidity in fact helped to steady the head in the required position.

### *Statistical analysis*

For energy metabolism, two groups were compared (5 healthy volunteers and 4 patients). Since multiple comparison corrections need to be taken into account (10 ROI values for each of the three functions in 1 subject), it was thought inappropriate to apply numerical statistical tests in view of the small number of subjects in the two groups. Instead, a mere description of the results is given in the text and in Tables 3 and 4. However, the frontal to occipital ratios were compared using a two-sample t test (Table 5). Equally, the ratios of striatal to surrounding brain radioactivity (determined by independent scans after L-($^{18}$F)fluorodopa administration) were compared using a two-sample t test.

TABLE 2 RATIO OF FLUORODOPA UPTAKE

| *Case no.* | *SRO syndrome patients* | *Healthy subjects* |
|---|---|---|
| 1 | 1.70 | 1.91 |
| 2 | 1.82 | 1.94 |
| 3 | 1.40 | 1.69 |
| 4 | 1.49 | 1.75 |
| 5 | 1 52 | 1.88 |
| Mean (±SD) | 1.59*<br>(±0.17) | 1.83<br>(±0.11) |

*$P = 0.025$ (t test) compared with healthy subjects.

## RESULTS

### *L-($^{18}$F)fluorodopa*

The curves of arterial plasma radioactivity had the same shape in patients and healthy subjects. At 120 min after injection of the tracer plasma activity in the patients was 5.7±1.2% of the peak value and in the healthy subjects 6.3±1.4%. Radioactivity uptake in nondopaminergic tissue ('surrounding brain') was similar in patients and healthy volunteers when comparing tissue curves normalized to arterial input of radioactivity.

The time-averaged ratio of activity between striatum and surrounding brain after L-($^{18}$F)fluorodopa administration in the healthy subjects was 1.83±0.11 (Table 2). Inspection of fig. 1 indicates that the ratio continued to increase with time between 120 and 180 min. In contrast the ratio in the patients was constant with time over the same period (which is also the case in patients with Parkinson's disease). The average ratio for the SRO syndrome patients was 1.59±0.17, which is significantly different from normal ($P = 0.025$; two sample t test). The distribution of the tracer throughout the plane in the patient group was similar to that in healthy subjects (fig. 2). During the first 10 min distribution of activity in the brain was that of blood volume. At later times the activity gradually became more diffusely distributed without a flow pattern visible at any time. No correlation between the striatum to surrounding brain ratio and the Webster scale score was found. However, the ratio seemed to become less with longer duration of disease (Table 6).

### *$CMRO_2$, CBF and OER*

Values of $CMRO_2$, CBF and OER for the healthy volunteers and patients are listed in Tables 3 and 4. The patients showed lower values for $CMRO_2$ in all brain

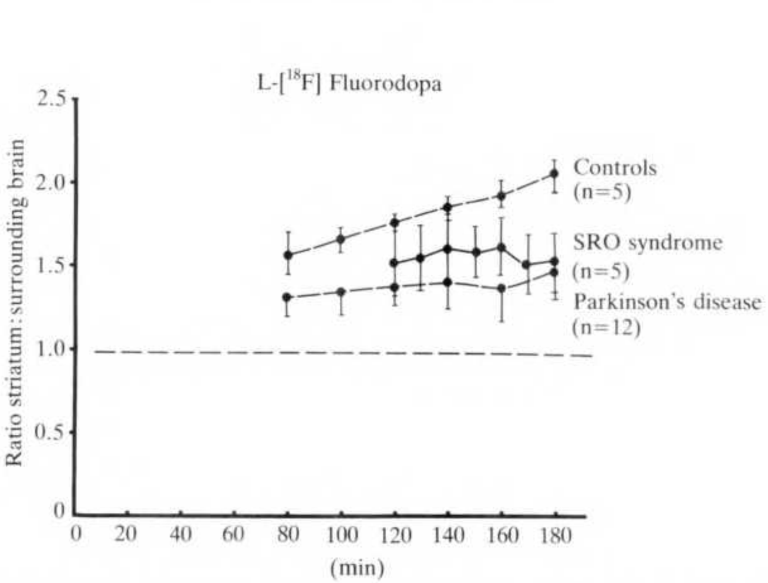

FIG. 1. Ratio of activity between striatum and surrounding brain over time after administration of L-($^{18}$F) fluorodopa. The data for the parkinsonian patients are taken from Leenders *et al.* (1986*b*).

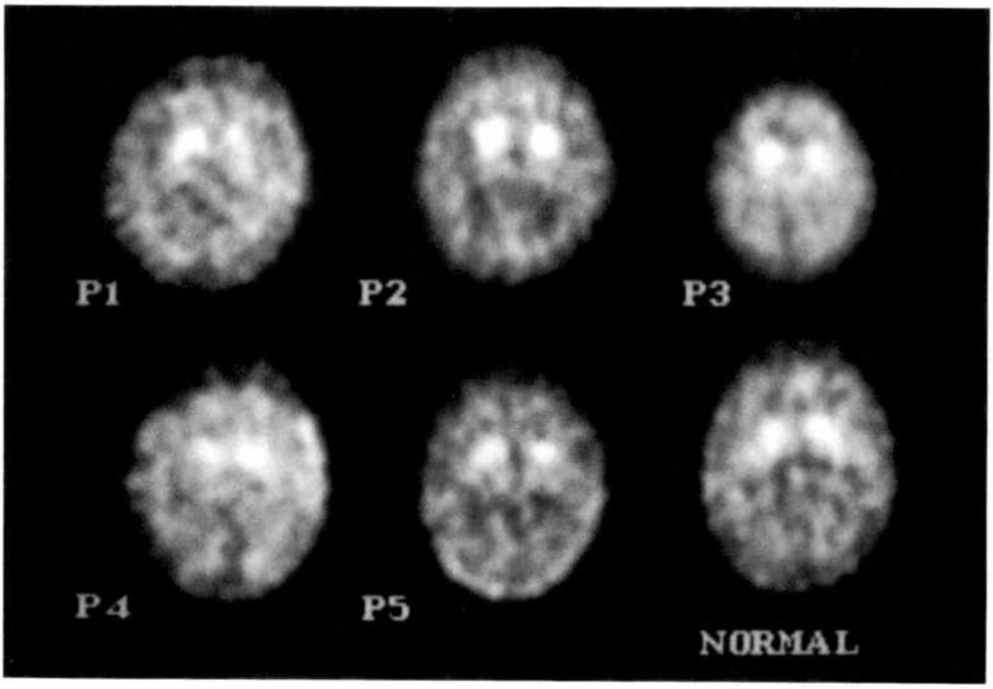

FIG. 2. Cross-sections of radioactivity distribution (summed images) after L-($^{18}$F)fluorodopa administration to the SRO syndrome patients (P1–P5) and 1 volunteer. The top of the image is frontal and the patient is viewed from above. The images are not scaled towards each other but to the maximum value of each image separately.

TABLE 3. MEAN (±SD) VALUES OF CEREBRAL PERFUSION AND OXYGEN METABOLISM (LOWER PLANE)

| | *Frontal cortex* | *Occipital cortex* | *Insular grey* | *Middle cerebral artery territory* | *Basal ganglia* |
|---|---|---|---|---|---|
| CMRO$_2$ | | | | | |
| Healthy subjects | 2.95±0.32 | 3.51± 0.42 | 3.46± 0.42 | 2.91±0.30 | 2.91±0.43 |
| SRO patients | 2.24±0.22 | 2.83± 0.37 | 2.53± 0.35 | 2.32±0.41 | 2.26±0.36 |
| Percentage | 76 | 81 | 73 | 80 | 78 |
| CBF | | | | | |
| Healthy subjects | 45.4 ±9.5 | 47.7 ±10.0 | 55.3 ±12.0 | 44.9 ±8.2 | 43.5 ±9.1 |
| SRO patients | 25.0 ±5.6 | 29.4 ± 6.1 | 28.7 ± 7.5 | 25.3 ±4.5 | 25.6 ±5.4 |
| Percentage | 55 | 62 | 52 | 56 | 59 |
| OER | | | | | |
| Healthy subjects | 39.5 ±6.5 | 44.2 ± 6.5 | 37.6 ± 5.6 | 39.1 ±5.0 | 39.6 ±5.4 |
| SRO patients | 46.9 ±7.3 | 50.3 ± 7.4 | 46.3 ± 8.0 | 47.2 ±7.1 | 49.2 ±8.5 |
| Percentage | +20 | +14 | +23 | +21 | +24 |

CMRO$_2$ = cerebral metabolic rate of oxygen. ml/100 ml/min CBF = cerebral blood flow. ml/100 ml/min. OER = oxygen extraction ratio: expressed as a percentage.

TABLE 4 MEAN (±SD) VALUES OF CEREBRAL PERFUSION AND OXYGEN METABOLISM (HIGHER PLANE)

| | *Frontal cortex* | *Occipital cortex* | *Parietal cortex* | *Middle cerebral artery territory* | *White matter* |
|---|---|---|---|---|---|
| CMRO$_2$ | | | | | |
| Healthy subjects | 2.81±0.43 | 3.16± 0.53 | 2.52±0.24 | 2.66±0.43 | 1.32±0.09 |
| SRO patients | 2.25±0.27 | 3.07± 0.37 | 2.42±0.39 | 2.44±0.41 | 1.06±0.23 |
| Percentage | 80 | 97 | 96 | 92 | 80 |
| CBF | | | | | |
| Healthy subjects | 45.3 ±9.9 | 45.1 ±11.1 | 36.9 ±7.0 | 40.6 ±6.4 | 21.4 ±3.3 |
| SRO patients | 25.6 ±3.5 | 33.5 ± 5.6 | 26.7 ±6.3 | 27.3 ±5.4 | 14.3 ±1.6 |
| Percentage | 57 | 74 | 72 | 67 | 67 |
| OER | | | | | |
| Healthy subjects | 37.5 ±6.0 | 42.5 ± 8.9 | 41.5 ±8.8 | 38.9 ±6.7 | 35.6 ±6.1 |
| SRO patients | 45.2 ±4.5 | 47.1 ± 4.3 | 46.8 ±4.6 | 46.2 ±5.2 | 39.1 ±8.5 |
| Percentage | +20 | +11 | +13 | +19 | +10 |

*See* Table 3 for comments

regions of the lower plane (73–81% of control values), although more pronounced in the frontal and temporal cortex. At the higher plane the values of CMRO$_2$ in the patients were on average 80% of control values in frontal cortex and white matter regions but normal in the other regions. CBF values in the patient group showed an even larger deviation from normal in all regions of both planes. The decreases were also more marked in the frontal regions. The larger decreases of CBF compared to that of CMRO$_2$ in the patients was counterbalanced by an increased oxygen extraction in all regions. The increase of OER varied between

10 and 24% and indicated a resetting of the flow/metabolism couple. The average arterial $pCO_2$ in the patients was 36.6 ± 2.9 mmHg and in the healthy volunteers 42.0 ± 1.4 mmHg.

The averaged ratio of frontal to occipital values for each function for both planes in both groups of subjects is listed in Table 5. For healthy subjects this ratio was below 1, mostly between 0.9 and 1 (one value was 0.84).

TABLE 5. FRONTAL TO OCCIPITAL RATIOS

| | *CMRO₂* | *CBF* | *OER* |
|---|---|---|---|
| Healthy subjects (n = 5) | | | |
| Lower plane | $0.84 \pm 0.03$ | $0.96 \pm 0.13$ | $0.89 \pm 0.11$ |
| Higher plane | $0.90 \pm 0.09$ | $1.02 \pm 0.11$ | $0.89 \pm 0.07$ |
| SRO patients (n = 4) | | | |
| Lower plane | $0.80 \pm 0.04$ | $0.86 \pm 0.07$ | $0.94 \pm 0.10$ |
| Higher plane | $0.74^{*} \pm 0.06$ | $0.77^{**} \pm 0.05$ | $0.96 \pm 0.02$ |

* $P < 0.025$; ** $P < 0.005$ compared with healthy subjects (t test). Values are given as mean and SD.

The frontal to occipital ratios for $CMRO_2$ and CBF in the patients were significantly lower than control values only in the higher plane (Table 5) corresponding to frontal cortex. As the occipital values vary little between the two planes, this was due principally to a relative decrease in frontal metabolism. Fig. 3 illustrates the differences in CBF between 2 SRO syndrome patients and 2 healthy subjects at the lower plane. No correlation between the WAIS score and frontal $CMRO_2$, CBF or frontal/occipital ratios was found. However, a good correlation was found between the duration of the disease and the absolute values of frontal $CMRO_2$: for the 4 SRO syndrome patients in which measurements were made durations of the disease were 3, 5, 5 and 6 yrs, respectively, and the corresponding $CMRO_2$ (higher plane) were 2.59, 2.30, 2.12 and 2.00 ml/100 ml/min. Patients with a low ratio of fluorodopa activity in striatum to that in surrounding brain had a tendency to lower frontal to occipital ratios of CBF (Table 6).

## DISCUSSION

We have investigated regional brain metabolism in 5 patients with the Steele-Richardson-Olszewski (SRO) syndrome using positron emission tomography (PET). The clinical syndrome was defined as a progressive nonfamilial multisystem degenerative disorder which begins after 50 yrs and includes amongst its symptoms a supranuclear downgaze palsy and at least two of the following: (1) axial dystonia with rigidity in extension; (2) frontal lobe syndrome; (3) bradykinesia/rigidity; (4) pseudobulbar palsy; (5) impaired postural reflexes with frequent falls. The clinical

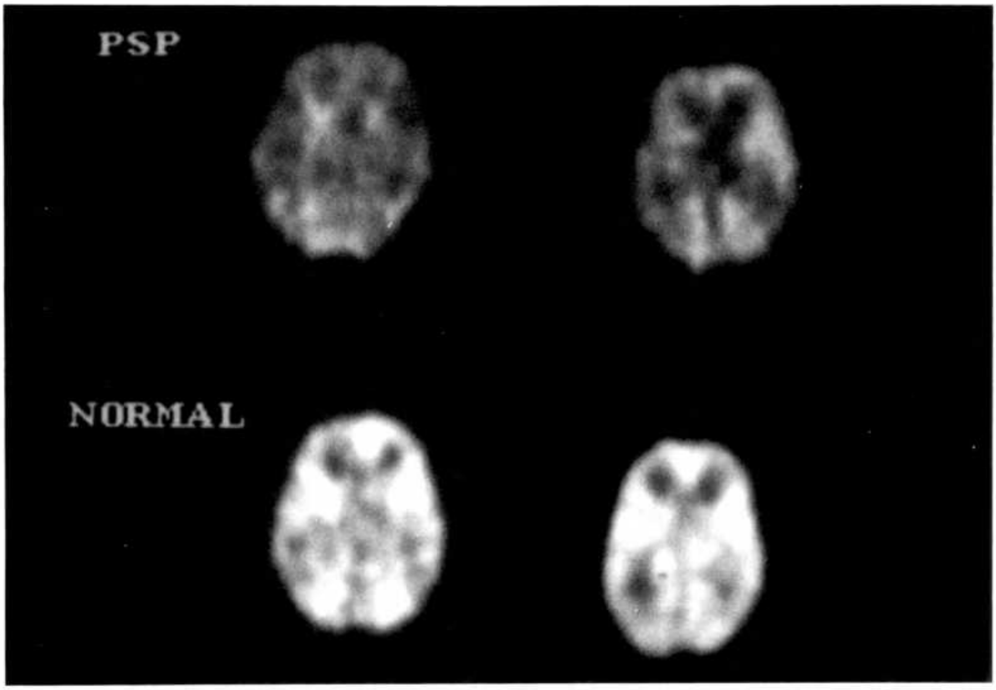

FIG. 3. CBF displayed at the lower plane of 2 SRO syndrome patients and 2 healthy subjects. Orientation of the images as in fig. 2.

TABLE 6. RELATION BETWEEN FLUORODOPA UPTAKE, HYPOFRONTALITY AND DURATION OF DISEASE IN SRO PATIENTS

| *Case no.* | *Duration of disease (yrs)* | *Frontal to occipital ratio CBF* | | *Ratio fluorodopa* |
|---|---|---|---|---|
| | | *Lower plane* | *Higher plane* | |
| 1 | 3 | 0.94 | 0.79 | 1.70 |
| 2 | 5 | 0.89 | 0.82 | 1.82 |
| 3 | 5 | 0.79 | 0.77 | 1.40 |
| 4 | 6 | 0.80 | 0.70 | 1.49 |

features and natural history of the SRO syndrome have recently been reanalysed in 52 patients by Maher and Lees (1986).

A striking finding of the patients' PET investigations is the global impairment of CBF and $CMRO_2$ in the patients' cerebral hemispheres. The decreases are most pronounced in the frontal and 'insular grey' regions (the latter region centres on the maximum metabolic activity recorded from the convolutions of the insular gyri and subcortical grey matter).

The same pattern of hypometabolism was found by D'Antona *et al.* (1985) who measured brain glucose utilization using PET in 6 patients with a probable SRO syndrome. They also stressed frontal hypometabolism. However, inspection of the published data (absolute values in their Table 3) reveals that mean glucose utilization was decreased in all investigated regions but reached statistical significance only in frontal regions. The marked frontal hypometabolism found in the study of D'Antona *et al.* and our own fits with the frontolimbic dementia which is found in the majority of cases of the SRO syndrome (Cambier *et al.*, 1985; Maher *et al.*, 1985). The dementia of the SRO syndrome is characterized by slowed mentation, difficulty in switching conceptual sets with perseveration and emotional or personality changes in the absence of dysphasia, agnosia and perceptual abnormalities.

We found no association between the degree of impaired frontal oxygen utilization and the WAIS psychological test scores. These tests, though not the most appropriate to assess 'frontal lobe function', were the only tests available in all our patients. However, D'Antona *et al.* (1985) also found no correlation between frontal glucose utilization and 'frontal lobe function'. This may be due to the small number of patients investigated in both studies. In addition, 2 of our patients (Cases 4, 5) had their psychological tests 6 and 9 months before their PET investigations. Alternatively, cortical oxygen or glucose metabolism may not be linearly related to intellectual function. Globus *et al.* (1985) did not find a correlation between the magnitude of regional cortical CBF reduction and severity of intellectual deterioration in 49 patients with Parkinson's disease. However, CBF measurements have the additional problem of a possible mismatch with energy metabolism in pathological conditions. This makes it even more difficult to interpret comparison of CBF with the level of intellectual functioning than is already the case for $CMRO_2$.

On the other hand, in our study duration of disease was directly correlated with the degree of frontal $CMRO_2$ reduction in the 4 patients investigated. Although the number of patients is small, this may indicate that impairment of oxygen metabolism reflects an overall decrease in neuronal function. CBF was decreased more than $CMRO_2$ (which resulted in an increased OER in all brain regions) and may partially be explained by the mean arterial $pCO_2$ of 36.6 mmHg (Rhodes *et al.*, 1981). However, apart from CBF reduction due to diminished demand by the tissue (decreased neuronal function) and lower $pCO_2$, a direct neuronal influence on the cerebral vasculature may contribute to the decrease of CBF in the patients. In the SRO syndrome the main location of pathology is in brainstem nuclei (Steele *et al.*, 1964; Jellinger *et al.*, 1980) and it is tempting to explain functional disturbances in the cerebral hemispheres by the subcortical lesions, a hypothesis that is also discussed by D'Antona *et al.* (1985). The additional decrease in CBF could be due to alterations in central control of vessel calibre, for example through diminished dopaminergic innervation of the cerebral vasculature. Destruction of the nucleus basalis of Meynert, which projects extensively to the cerebral cortex and which is also damaged in the SRO syndrome, induces widespread reduction in cortical glucose utilization in rats (London *et al.*, 1984). This would also explain the decreased choline acetyl transferase (CAT) activity in the frontal cortex found by Ruberg *et al.* (1985) in postmortem brains of 9 SRO syndrome patients. These authors also showed that dopamine and homovanillic acid concentration were reduced in the corpus striatum (but not in the cerebral cortex) to levels comparable to those found in Parkinson's disease.

In the SRO syndrome the nigrostriatal dopaminergic system is severely affected, which is confirmed by the diminished striatal uptake of the levodopa analogue L-($^{18}$F)fluorodopa in our study (Table 2, fig. 1). The decreased processing of this tracer by the striatum was paralleled by decreases in frontal CBF (Table 6). In contrast to Parkinson's disease, the dopaminergic mesocortical pathway appears to be spared in the SRO syndrome, at least as judged by neurochemical studies, suggesting that damage to this ascending pathway to frontolimbic striatum may not be responsible for the dementia (Ruberg *et al.*, 1985). Cortical accumulation of L-($^{18}$F)fluorodopa could not be assessed by the present study due to inadequate spatial resolution of the tomograph used.

No effect of age on the ratio of L-($^{18}$F)fluorodopa uptake was seen in the 5 healthy subjects whose range of age was from 30 to 64 yrs. This is compatible with most studies reporting age changes in the human cerebral dopaminergic system. For example, there is a considerable decrease in tyrosine hydroxylase activity before the age of 20 yrs followed by relative stability during adulthood (McGeer *et al.*, 1977). This curvilinear age effect has also been shown by Wong *et al.* (1984) in vivo for human striatal dopamine $D_2$ receptor binding using $^{11}$C-N-methylspiperone and PET. However, 5 subjects are insufficient to assess age effects adequately, but they provide normal values in the relevant age group with which we compare the results obtained in our patients.

Since CBF in patients was lower than in the healthy subjects, it might be asked whether this contributed to the lower striatal L-($^{18}$F)fluorodopa uptake in patients. This, however, seems unlikely. First, only a small fraction of L-($^{18}$F)-fluorodopa is taken by the brain due to the low capacity of the blood-brain barrier transport system. In such a situation a flow component to uptake is small or insignificant. Indeed, the reconstructed images of radioactivity distribution during the first 10 min after L-($^{18}$F)fluorodopa administration (data not shown) yield a blood volume type of distribution and not one dependent on blood flow. Secondly, if CBF had an influence on L-($^{18}$F)fluorodopa brain tissue uptake, it would influence uptake by both striatal and surrounding tissue as CBF was decreased globally in SRO patients. Therefore, the ratio of radioactivity between the two regions would be little influenced by this. Thirdly, L-($^{18}$F)fluorodopa uptake in nonstriatal tissue is not decreased in patients with Parkinson's disease who also show a global decrease of CBF (Wolfson *et al.*, 1985). Not only were the level and rate of disappearance of radioactivity in surrounding brain in parkinsonian patients (and also in the SRO patients presented here) similar to those in healthy subjects, but also L-($^{18}$F)fluorodopa influx measured by relating brain tissue radioactivity to arterial plasma radioactivity showed no difference in nonstriatal tissue between the patients with Parkinson's disease and healthy volunteers (Leenders *et al.*, 1986*c*).

Choline acetyltransferase activity and tritiated spiperone binding were also reported to be reduced in the striatum of the 9 SRO syndrome patients in the study of Ruberg *et al.* (1985), confirming that striatal interneurons are directly involved in the pathological process. A decrease of 50% of labelled spiperone binding in striatum in postmortem studies of 5 SRO syndrome patients was previously reported by Bokobza *et al.* (1984) and confirmed in vivo by Baron *et al.* (1985) who studied 7 SRO syndrome patients using PET and the tracer ($^{76}$Br)-bromospiperone. This finding contrasts with the situation found in Parkinson's disease where the severe presynaptic dopaminergic lesion does not seem to affect striatal labelled methylspiperone binding (Leenders *et al.*, 1985*b*; Hägglund *et al.*, 1987). Furthermore, postmortem binding studies with labelled spiperone do not provide evidence for large changes in binding in untreated patients with Parkinson's disease (Bokobza *et al.*, 1984). This may well explain why dopamine agonists are beneficial in the early stages of Parkinson's disease but much less, if at all, in SRO syndrome patients (Klawans and Ringel, 1971; Haldeman *et al.*, 1981; Jackson *et al.*, 1983). In our study all 5 patients failed to respond to therapeutic doses of levodopa. Although the main site of the lesion in the SRO syndrome is without doubt the brainstem, the frontal cortex and hippocampus are probably also directly involved to some extent. Mild cortical atrophy is sometimes visible on CT scans, as in our patients (Table 1) and reported elsewhere (Haldeman *et al.*, 1981). Spiperone binding, which is a postsynaptic function (Laduron *et al.*, 1978; Creese, 1982), is decreased in the frontal cortex in postmortem studies (Ruberg *et al.*, 1985). Although Baron *et al.* (1985) do not comment on cortical binding in their paper on ($^{76}$Br) bromospiperone binding in vivo using PET, there is a suggestion from their published image that binding is decreased in frontal cortex. Evidence of cell loss and tangle formation in cortical areas is available from postmortem studies (Steele, 1972).

This raises the issue of the classification of the SRO syndrome as a 'subcortical dementia' (Albert *et al.*, 1974). This form of dementia was defined on clinical grounds and shows striking similarity with the dementia which occurs after bilateral frontal lobe disease. In view of the marked subcortical pathology in the SRO syndrome it is postulated that the frontal lobe dysfunction in this condition may be caused by deactivation or disconnection from subcortical structures (Albert *et al.*, 1974; Cummings and Benson, 1984). The available PET tracer studies of the SRO syndrome patients (D'Antona *et al.*, 1985; Foster *et al.*, 1986; this paper) support the notion of extensive brainstem lesions expressing themselves in specific striatal and cortical functional changes. However, the name 'subcortical dementia' may be rather misleading as it suggests that the seat of this form of dementia is located in subcortical structures. It is clear from the PET studies that the development of the clinical signs and symptoms of this 'frontal lobe type of dementia' is associated with actual frontal lobe dysfunction. The difficulties connected with a strict separation of 'cortical' and 'subcortical' dementias are discussed by Whitehouse (1986).

It is clear, nevertheless, that PET, using a combination of several specific tracers, can demonstrate patterns of metabolic and neurotransmitter dysfunction which characterize different clinical conditions. Global decreases in CBF and energy metabolism are seen in all degenerative diseases but in the SRO syndrome there is a preferential frontal hypometabolism. Frontal hypometabolism has also been described in severe Alzheimer's disease by Frackowiak *et al.* (1981) and Duara *et al.* (1986). This contrasts with the situation in early Alzheimer's disease and parkinsonian dementia where a focal hypometabolic emphasis in the temporal/posterior parietal cortex predominates (Frackowiak *et al.*, 1981; Kuhl *et al.*, 1984). Presynaptic dopamine metabolism is severely impaired in both Parkinson's disease and SRO syndrome and can be demonstrated in vivo using L-($^{18}$F)fluorodopa and PET. Dopamine receptor binding in the striatum is decreased in SRO syndrome patients but is essentially normal in Parkinson's disease. In Huntington's disease L-($^{18}$F)fluorodopa uptake in the striatum is normal but (11-C)methylspiperone is decreased (Leenders *et al.*, 1986*a*) and in addition, caudate nucleus glucose metabolism is diminished focally (Kuhl *et al.*, 1982), and in later stages the frontal cortex may also show decreased values (Mazziotta *et al.*, 1985).

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# ACUTE TRANSCORTICAL MIXED APHASIA

## A CAROTID OCCLUSION SYNDROME WITH PIAL AND WATERSHED INFARCTS

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## SUMMARY

Four of 1 200 consecutive patients with their first stroke showed acute transcortical mixed aphasia (TMA) characterized by nonfluent speech with impaired naming, semantic paraphasias, echolalia, impaired comprehension, good repetition, reading, and writing on dictation. All 4 had left internal carotid artery (ICA) occlusion with ipsilateral anterior pial territory infarction (precentral-central sulcus artery territory) and watershed infarction between the middle and posterior cerebral artery territories, which spared and 'isolated' the perisylvian speech areas. Although rare, acute TMA is highly suggestive of infarction due to ICA occlusion, in that it is probably related to simultaneous embolism (anterior pial infarction) and haemodynamic insufficiency (posterior watershed infarction).

## INTRODUCTION

Although the concept of transcortical aphasia goes back to Wernicke (1874), it was Kurt Goldstein (1917) who first used this terminology to describe speech disturbances which do not involve the elementary components of language. Spontaneous speech and verbal outflow may be decreased (transcortical motor aphasia) or comprehension may be impaired (transcortical sensory aphasia), but typically there is no agrammatism or syntax dysfunction, and no phonemic paraphasia, with a remarkable sparing of the abilities of verbal reproduction, such as repetition and dictation. The preservation of the elementary components of speech corresponds anatomically to the absence of involvement of the perisylvian speech areas, including Broca's area, Wernicke's area, the arcuate fasciculus and Heschl's gyrus. In transcortical motor aphasia, there is an interruption of the connections between the supplementary motor area and Broca's area, usually from a lesion anterolateral to the left frontal horn (Mazzocchi and Vignolo, 1979; Freedman *et al.*, 1984). In transcortical sensory aphasia, the lesion may be parieto-occipital (posterior cerebral artery territory) or posterior parietal (watershed area between the posterior and middle cerebral artery territories) (Kertesz *et al.*, 1982; Bogousslavsky and Regli, 1986*a*). In the mixed form (TMA), the motor and

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sensory components combine and yield a characteristic speech disorder, with nonfluent spontaneous speech, poor naming and comprehension, but good repetition. In this aphasia, in which there is no reciprocal access between the words processed phonemically and the semantic processing (Heilman *et al.*, 1976, 1981), the speech areas may be considered to be 'isolated' from the rest of the brain. It has been termed the syndrome of isolation (Geschwind *et al.*, 1968), or deactivation (Cambier *et al.*, 1980) of the speech areas. This rare syndrome has been studied mainly in its chronic form related to diffuse brain processes, in global aphasia evolving towards TMA, or in patients with recurrent strokes (Geschwind *et al.*, 1968; Brown, 1975; Whitaker, 1976; Cambier *et al.*, 1980; Assal *et al.*, 1983; Speedie *et al.*, 1984). We have studied 4 patients who demonstrate that TMA may occur acutely, in the context of an acute ischaemic stroke. The typical finding of two independent infarcts in the left hemisphere, which had a similar topography in all 4 cases, together with the presence of an occlusion of the ipsilateral internal

TABLE. CHARACTERISTICS OF APHASIA

| | *Case 1* | *Case 2* | *Case 3* | *Case 4* |
|---|---|---|---|---|
| Spontaneous speech | Reduced (sentences not more than 3 words) | Isolated words | Reduced (sentences not more than 4 words) | Absent |
| Semantic paraphasia | + | + | + | + (often 'aberrant') |
| Phonemic paraphasia | — | — | — | — |
| Dysarthria | — | — | — | — |
| Voice volume | Normal | Normal | Normal | Normal |
| Naming[1] | 1/76 | 0/76 | Absent or semantic paraphasias (Boston Test not done) | 0/76 |
| Repetition[3] | | | | |
| Series of 3–8 phonemes | Normal | Normal for series of 5 items, tendency to repeat only end of series of >5 items | Normal | Normal for series ≤4–5 items, tendency to repeat end of series |
| Series of 3–5 words | Normal | | Normal | |
| Series of 3–10 words | Normal | | Normal | |
| Echolalia | + | + | + | + |
| Auditory comprehension[2] | 0/36 | 0/36 | Only simple orders (Token Test not done) | Only simple orders, 4/36 |
| Spontaneous writing | Only his name | Absent | Absent | Absent |
| Dictation | Few omissions or perseveration of letters | Normal | Normal | Normal |
| Reading | | | | |
| Letters | Normal | Normal | Normal | Normal |
| Text | Normal except slight hemineglect, but no understanding | Normal, but no understanding | Normal, but no understanding | Normal, but no understanding |

[1] Boston Naming Test (Kaplan *et al.*, 1976). [2] Token Test (De Renzi and Vignolo, 1962). [3] Batterie des examens neuropsychologiques du CHUV (Assal, 1985).

carotid artery (ICA), suggest that acute TMA may be specific of stroke due to ICA occlusion with simultaneous embolization and haemodynamic failure.

## PATIENTS

The 4 patients were French-speaking. They were selected from among 1 200 patients with a first stroke admitted consecutively to our service over a 6-yr period. They corresponded to 2.4% of the 170 stroke patients with ipsilateral ICA occlusion. This proportion is accurate as all stroke patients undergo a standard protocol of investigations, including Doppler ultrasound with frequency analysis. Cerebral CT, ECG, standard blood tests, ECG monitoring and, when indicated, echocardiography are also performed systematically. Every patient with a supratentorial stroke undergoes neuropsychological testing, using a standard battery of tests (Assal, 1985). TMA was defined as a nonfluent aphasia with impaired naming, semantic but no phonemic paraphasia, and no dysarthria, together with impaired comprehension with or without an echolalic tendency, and good repetition, reading and writing on dictation (though without understanding). The topography of pial territory infarcts on CT was evaluated following the guidelines of Damasio (1983). Our method for diagnosing borderzone infarction between the territory of the middle, anterior and posterior cerebral arteries (watershed infarcts) has been detailed elsewhere (Bogousslavsky and Regli, 1986*b*). One patient (Case 1) has been published previously with a detailed neuropsychological study (Bogousslavsky *et al.*, 1985).

### *Case reports*

*Case 1.* A 68-yr-old right-handed man with atrial fibrillation for 3 yrs suddenly lost consciousness. When he regained consciousness a few minutes later, he had right-sided weakness and speech disturbances. On admission, blood pressure was 140/90 mmHg and he had an irregular pulse (100/min) due to atrial fibrillation. He had a moderate right hemiparesis involving the face and

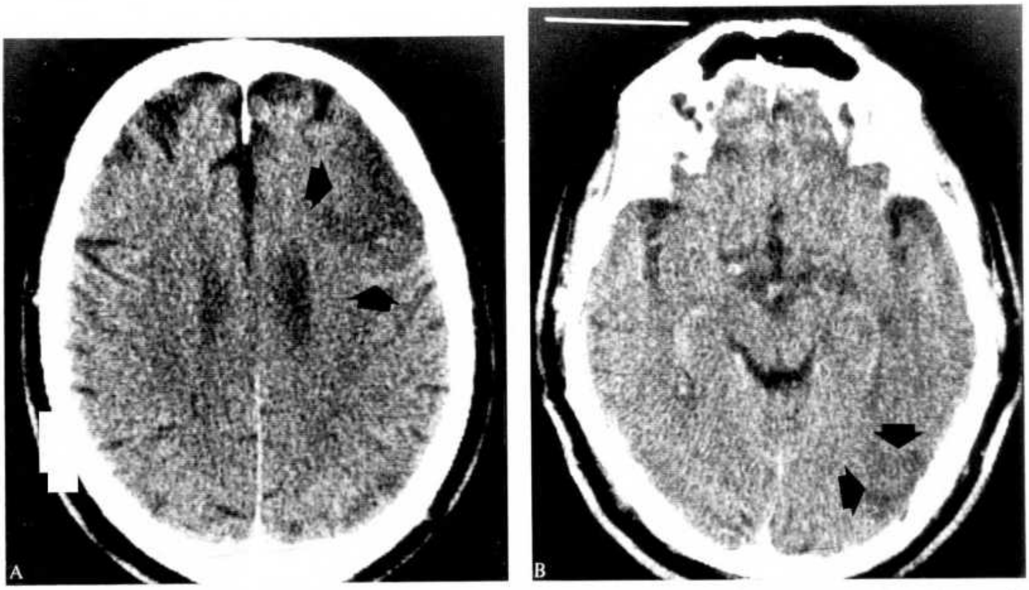

FIG. 1. CT scan. *Case 1.* A, infarct in the territory of the left precentral artery. B, watershed infarct between the territory of the left middle and posterior cerebral arteries (arrows).

upper limb, with hyperactive tendon reflexes. The plantar response was flexor on the left, and indifferent on the right. Tactile and pain sensation were mildly decreased in the right side of the face. On unilateral visual stimulation, no hemianopia was present, but he had right visual extinction on double simultaneous visual stimulation, and he tended to neglect visual information in the right hemispace. Spontaneous speech was markedly reduced and the patient did not produce sentences of more than 3 words ('je veux manger', i.e., 'I want to eat'), with several semantic paraphasias. Object naming was much impaired (1/76, Boston Naming Test), with semantic paraphasias ('stylo' (pen) instead of 'maison' (house), 'chaise' (chair) instead of 'table' (table)). This contrasted with full preservation of the repetition of phonemes and short and long (10 words: 'il fait beau aujourd'hui et j'aimerais aller me promener dehors') sentences; moreover, there was a tendency to repeat every word or sentence pronounced by the examiner. Comprehension was severely disturbed (0/36, Token Test) and echolalia usually replaced the execution of orders. Reading was spared, except for some omissions due to hemineglect. Writing with the left hand on dictation showed only rare letter omissions or perseverations, but spontaneously the patient wrote only his name. A CT scan on admission was normal, but 1 wk later showed 2 superficial infarcts in the left hemisphere, 1 in the superior-posterior part of the frontal lobe (precentral artery territory), and 1 in the posterior parietal region (watershed territory) (fig. 1). On Doppler ultrasound with frequency analysis, the left ICA was not detected and the flow was decreased in the ipsilateral ophthalmic artery, with increase after compression of the ipsilateral superficial temporal artery. Echocardiography showed left atrial enlargement without thrombus. Standard blood tests were unremarkable, except for a haematocrit at 0.47. Within 2 wks, the patient improved markedly and on discharge he had only a slight pronator drift on the right, with decreased spontaneous speech, object-naming difficulties with semantic paraphasias and moderate comprehension impairment (24/36, Token Test).

*Case 2.* A 72-yr-old right-handed man, who was a smoker and had been hypertensive for 10 yrs, had an episode of right facial weakness with dysarthria for 2 h. This was followed 4 days later by shaking of the right hand for 10 min and inability to speak. On admission, blood pressure was

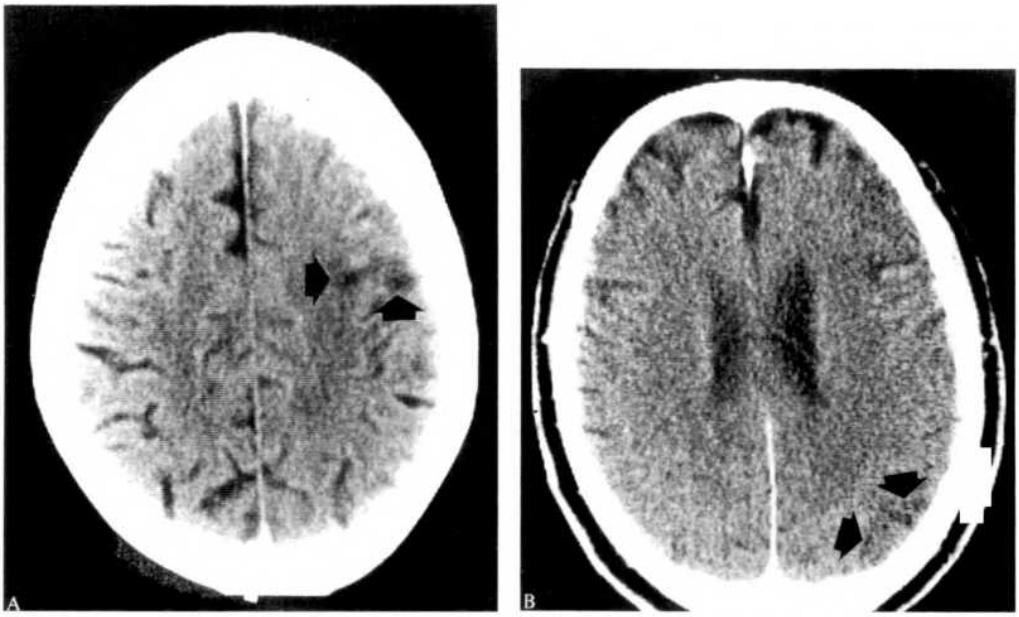

FIG. 2. CT scan with contrast, *Case 2.* A, infarct in the territory of the precentral-central artery branches on the left. B, watershed infarct between the territory of the left middle and posterior cerebral arteries (arrows).

160/80 mmHg, with a regular pulse (80/min). A mild faciobrachiocrural hemiparesis was present, with an extensor plantar response on the right. The visual fields could not be examined because of lack of comprehension. No hemisensory defect was noted. There was a left Horner's syndrome with miosis and narrowing of the palpebral fissure. Only isolated words were produced spontaneously. Object naming was absent or yielded semantic paraphasias ('bibelot' (curio) instead of 'aquarium', 'car' (bus) instead of 'train'). The repetition of phonemes, words and sentences was normal for short items, but with words of more than 5 phonemes and sentences of more than 5 words, the patient tended to repeat only the last part of the word or of the sentence. Comprehension was nil (0/36, Token Test), and was often replaced by echolalia. Reading was slowed but otherwise normal, but the patient had no understanding of the text. He did not write spontaneously, but on dictation (sentences up to 5 words) the only abnormalities were related to the right-sided weakness. A CT scan performed 1 day after admission showed 2 superficial infarcts in the left hemisphere, 1 cortical-subcortical in the superior and posterior frontal region (precentral artery-central sulcus artery territory), and 1 in the posterior parietal region (watershed territory) (fig. 2). Doppler ultrasound and digital intra-arterial angiography showed occlusion of the left internal carotid artery without reversed ophthalmic flow. Because of poor resolution, the collateral circulation to the left hemisphere could not be adequately assessed. ECG showed flat or inverted T waves in I, II, III, aVL, aVF. The fasting blood cholesterol concentration was 7.3 mmol/l and the haematocrit 0.48. On discharge 3 wks later, there was only a mild pronator drift and the aphasia had improved (more fluent spontaneous speech, Token Test 14/36, object naming showing only episodic semantic paraphasias). As comprehension improved and the visual fields could be assessed, a lower right quadrantanopia was demonstrable.

*Case 3.* A 59-yr-old right-handed man without known risk factors except for cigarette smoking was admitted 2 days after he experienced moderate left frontotemporal headaches with speech disturbances and tingling in the right index finger. On admission, his blood pressure was 180/100 mmHg, with a regular pulse (86/min). He had bilateral carotid bruits. There was a mild right lower

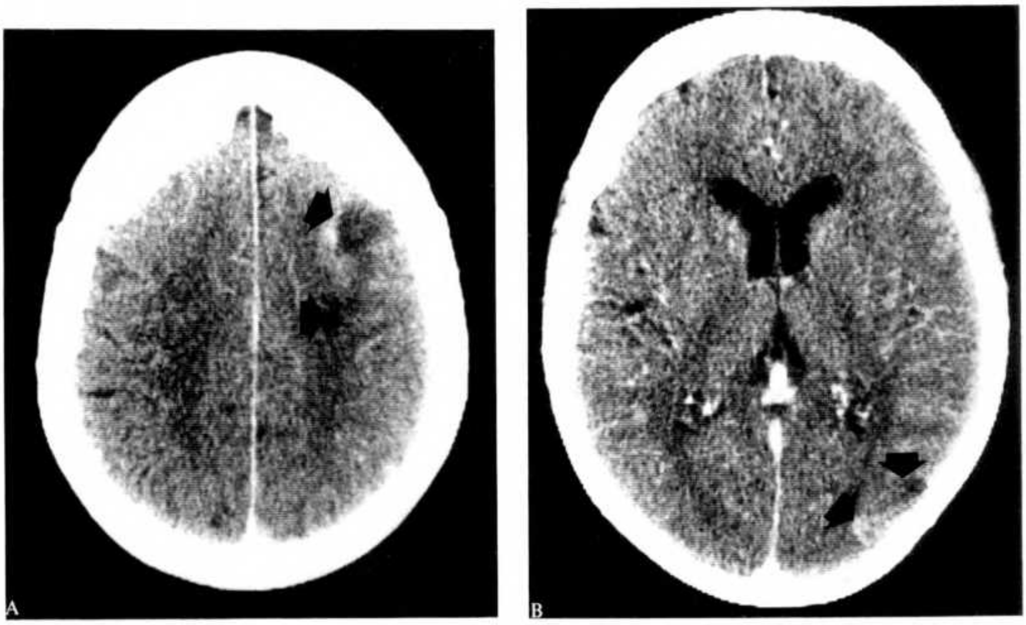

FIG. 3. CT scan with contrast, *Case 3.* A, infarct in the territory of the precentral-central artery branches on the left. B, watershed infarct between the territory of the left middle and posterior cerebral arteries (arrows).

facial weakness and a right pronator drift, with normal tendon reflexes and flexor plantar responses. Tactile, pain, temperature, vibration and position sensation was slightly decreased on the right side of the body with decreased abdominal reflexes on that side. A lower right quadrantanopia was present. There was no dysarthria, but the patient did not produce sentences of more than 4 words and had word-finding difficulties ('maisonnée' (house) instead of 'bibliothèque' (library), 'piscine' (swimming pool) instead of 'aquarium'). Naming was replaced by semantic paraphasias or was absent. There was no agrammatism, but the sentences were meaningless. He could comprehend only very simple orders, such as 'close your eyes' or 'open your mouth'; more complex orders were not executed, and the patient tended to repeat the order. Repetition of isolated phonemes and words and of sequences (3–8 items) was normal. Reading of a text was normal, but retrieval of its meaning was impossible. The patient did not write spontaneously, but there was no impairment on dictation. A CT scan on the day of admission showed 2 superficial infarcts in the left hemisphere, 1 in the posterior prefrontal region (precentral artery territory), and 1 in the posterior parietal region (watershed territory) (fig. 3). Doppler ultrasound with frequency analysis showed no diastolic flow in the left common carotid artery, no detection of the left ICA, with reversed ipsilateral ophthalmic flow ipsilaterally, and increased systolic peak frequency (8–9 kHz) in the right ICA suggesting 75% stenosis; on transcranial Doppler, the flow velocity was decreased on the left as compared to the right (32 cm/s vs 50 cm/s). The retinal artery pressure was decreased on the left (60/30 mmHg vs 80/60 on the right). An ECG showed diffuse ischaemic changes. The haematocrit was 0.47, but other routine blood tests were normal. Over the following few days, the patient improved remarkably and, on discharge, one month later, there was only a slight pronator drift, with isolated word-finding difficulties and rare semantic paraphasias; verbal fluency and comprehension had returned to normal.

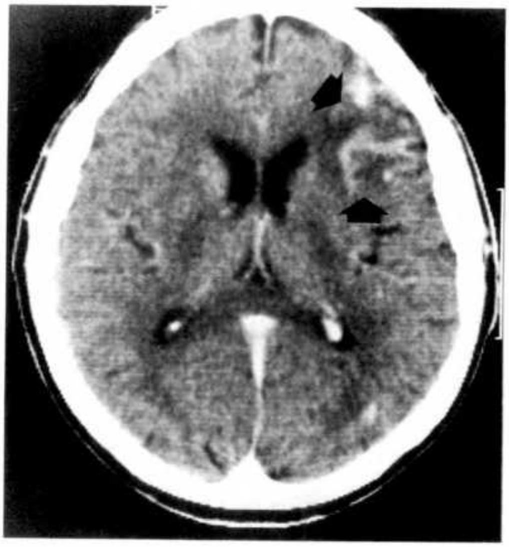

FIG. 4. CT scan with contrast, *Case 4*, showing enhancing infarcts (arrows) in the precentral artery territory and in the posterior watershed area on the left.

*Case 4*. This 66-yr-old right-handed man was a smoker and had known hypercholesterolaemia. During a walk in the mountains, he suddenly experienced right-sided weakness and was unable to speak for 15 min. This initial muteness was followed by the development of abnormal speech, which seemed 'incoherent' or 'confused' to his wife, without deformed words. On admission 18 h later, his blood pressure was 140/90 mmHg, with a regular pulse (76/min). There was a mild right lower facial weakness with downward drift of the outstretched right arm. The tendon reflexes were increased in the right upper limb. The plantar responses were flexor. Within the limits of the comprehension disturbances, sensation seemed unimpaired. The patient did not speak spontaneously. Object naming was nil: either the patient could not find any word or he made a semantic paraphasia which was often 'aberrant' (e.g., 'elephant' instead of 'watch'). There was no dysarthria and no phonemic paraphasia. Only simple orders were executed ('open your mouth', 'close your eyes'). More complex orders were repeated but not executed. The repetition of series of phonemes or words of up to 5 items was normal, but with longer series, the patient tended to repeat only the 4 or 5 last items. Reading was performed only on vigorous verbal and visual stimulation by the examiner, but the meaning of the text was not understood. The patient did not write spontaneously but on dictation or on copying a text; he made no errors. A CT scan on the day of admission showed 2 superficial infarcts in the left hemisphere, 1 in the middle posterior region of the frontal lobe (precentral artery-central sulcus artery territory), and a smaller one involving the cortex of the posterior parietal region (watershed territory). On Doppler ultrasound with frequency analysis, there was a decreased systolic peak and no diastolic flow in the left common carotid artery, and no detection of the left ICA, with reversed ipsilateral ophthalmic flow. An ECG and routine blood tests were normal; haematocrit was 0.45. Within 3 wks, the speech disturbances improved, with recovery of some spontaneous speech, object naming (Boston Naming Test 25/76), and comprehension (Token Test 15/36). Echolalia had disappeared. The neurological examination was normal.

## DISCUSSION

In our 4 patients, the most striking disturbance was acute TMA, which was associated with some degree of hemiparesis, hemisensory impairment or hemianopia. TMA seems to be a very uncommon manifestation of stroke, as it was not reported in any of 411 patients with a vascular lesion in the dominant hemisphere on CT who had neuropsychological testing (Barat *et al.*, 1978; Mazzocchi and Vignolo, 1979; Basso *et al.*, 1985). The first report of a patient with speech disturbances suggestive of TMA seems to be that by Hübner (1889), who studied a 64-yr-old man who had a transient loss of speech which recurred 1 month later; on examination, spontaneous speech was reduced to 'ja, jawohl, nunja', and there was loss of comprehension of spoken and written language contrasting with good repetition, writing spontaneously and on dictation, and reading. At autopsy, some cortical atrophy was noted, and the patient had 3 infarcts in the left hemisphere, 2 superficial (1 in the posterior-inferior part of the parietal lobe, 1 at the sylvian edge of $F_3$, 1 in the lenticulocapsular region); the state of the cerebral arteries was not mentioned. Cambier *et al.* (1980) reported a 60-yr-old man who suffered a left anterior capsular infarct followed 2 months later by a second stroke with extension of the first lesion; a posterior watershed infarct was also visible on the CT scan. TMA was observed after the second stroke. Ross (1980) reported a 52-yr-old man with a subarachnoid haemorrhage due to a ruptured anterior communicating artery aneurysm, whose CT scan showed extensive infarction in the left anterior cerebral artery territory; he suggested that the motor component of TMA was due to involvement of the left supplementary motor area and that the sensory component was due to involvement of the left supplementary sensory area. However, the extent of brain damage was difficult to assess in this patient with severe subarachnoid bleeding, and it must be emphasized that TMA has not been reported in any other patient with an infarct limited to the left anterior cerebral artery territory, even when both motor and sensory supplementary areas are involved (Környey, 1975; Bogousslavsky *et al.*, 1987*b*). Ross's patient was initially unconscious, then had global aphasia, and TMA was observed only 4 months later (it was not acute). In all other reported cases of TMA in cerebral ischaemia, large, diffuse, often bilateral lesions were present (though the perisylvian speech areas were completely or partially spared), and TMA usually developed after a phase of global aphasia (Geschwind *et al.*, 1968; Brown, 1975; Whitaker, 1976; Assal *et al.*, 1983; Speedie *et al.*, 1984). In one patient, the cause was carbon monoxide intoxication (Geschwind *et al.*, 1968), but it was unclear in the other patients, in whom no information on the state of the cerebral arteries was given. Transcortical features have been reported in aphasia due to subcortical stroke with lenticulocapsular or thalamic involvement (Mohr *et al.*, 1975; Cappa and Vignolo, 1979; McFarling *et al.*, 1982; Puel *et al.*, 1984; Bogousslavsky *et al.*, 1986*c*). However, in this setting, the aphasia differs from TMA by a decrease in voice volume, only slight comprehension impairment, and frequent disturbance of articulation and prosody, so that it has been called 'atypical aphasia' or 'dissident aphasia' (Damasio *et al.*, 1982; Hungerbühler *et al.*, 1984; Puel *et al.*, 1984).

Our findings suggest that acute TMA may be specific of stroke due to ICA occlusion. All 4 patients had a stereotyped topography of the 2 infarcts, which occurred simultaneously in the left hemisphere: one was anterior to Broca's area and was of pial territory type (precentral-central sulcus arteries territory), and the other was posterior to Wernicke's area and was watershed between the middle and posterior cerebral artery territory. Pial territory infarcts are usually embolic in ICA occlusion, occurring usually at the time of occlusion (Castaigne *et al.*, 1970; Pessin *et al.*, 1979). On the other hand, although embolism may account for rare cases of infarction in arterial borderzones (Torvik, 1984; Bogousslavsky and Regli, 1986*a*), most watershed infarcts are related to haemodynamic failure (Zülch, 1961; Adams *et al.*, 1966; Ross Russell and Bharucha, 1978). When unilateral, watershed infarcts are usually associated with severe stenosis or occlusion of the ipsilateral ICA, in up to 90% of the cases (Wodarz, 1980; Bogousslavsky and Regli, 1986*a*). The occurrence of simultaneous infarcts has usually not been emphasized in the series of patients with ICA occlusion examined by CT (Radü and Moseley, 1978; Takagi and Shinohara, 1981; Goto *et al.*, 1982; Ringelstein *et al.*, 1983; Bogousslavsky and Regli, 1984). But conditions other than ICA occlusion have never been reported to yield the simultaneous anterior pial and posterior watershed infarcts which may produce acute TMA, probably because any other condition is unlikely to cause embolism simultaneous to haemodynamic insufficiency in one hemisphere.

A syndrome other than acute TMA, global aphasia without hemiparesis, may be due to two infarcts occurring simultaneously in the dominant hemisphere (Van Horn and Hawes, 1982). It is usually due to two discrete pial territory infarcts involving Broca's and Wernicke's areas, but sparing the motor strip and corticospinal pathways (Damasio, 1981; Van Horn and Hawes, 1982; Tranel *et al.*, 1986). However, this syndrome may be due to causes of embolism other than ICA occlusion (Van Horn and Hawes, 1982; Legatt *et al.*, 1987). It may also occur from a single infarct in the dominant hemisphere (Ferro, 1983), and is even not specific of cerebral infarction (Legatt *et al.*, 1987).

On the other hand, another two-infarct syndrome, the opticocerebral syndrome, which is due to simultaneous watershed infarction in the brain and ipsilateral optic nerve head, is highly suggestive of ipsilateral ICA occlusion (Radovici and Lasco, 1948; Waybright *et al.*, 1982; Bogousslavsky *et al.*, 1987*a*). In stroke patients with ICA occlusions, acute TMA has the same prevalence as the opticocerebral syndrome (2.4%) (Bogousslavsky *et al.*, 1987*a*), and may be as specific for ICA occlusion. Although rare, acute TMA yields a characteristic aphasic picture. Its occurrence in acute stroke should point towards combined pial and watershed territory infarction in the setting of ICA occlusion, probably from simultaneous embolic and haemodynamic phenomena.

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# OPTIC ATAXIA: A SPECIFIC DISRUPTION IN VISUOMOTOR MECHANISMS

## I. DIFFERENT ASPECTS OF THE DEFICIT IN REACHING FOR OBJECTS

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## SUMMARY

Visually directed arm movements have been studied by film recordings in 10 patients with optic ataxia resulting from unilateral lesions of the parietal region, in 3 cases on the right and in 7 on the left. Half of the patients also underwent visuospatial perceptive tests. The results indicate the following. (1) Optic ataxia is a specific visuomotor disorder, independent of visual space misperception. (2) The proximal and the distal components of the movements are equally affected as shown in reaching and hand orientation tasks. (3) The percentages of spatial and orientation errors quantified, respectively, in these two situations show a different distribution across the different hand-field combinations according to the side of the lesion: whereas the right-damaged patients show a deficit essentially related to a field effect, the left-damaged patients show in addition to the latter an impairment related to a hand effect. These findings suggest that the 2 types of visuomotor mechanisms responsible for the proximal and distal components of visually-directed arm movements are controlled by the parietal cortex and that there should exist a hemisphere asymmetry in the functional organization of these mechanisms. (4) Reconstruction of the lesions drawn from CT scans in 8 of the patients shows a salient and constant involvement of the posterior parietal cortex, always including the intraparietal sulcus and either the superior part of the inferior parietal lobule or more often various parts of the superior parietal lobule. The weak co-occurrence of optic ataxia and hemispatial neglect, and their different lesion sites, indicate a double dissociation between these two symptoms.

## INTRODUCTION

Among the constellation of symptoms that reflect impaired spatially oriented behaviour in patients with parietal lesions, optic ataxia may appear as one of the most specific. Since Balint's famous observation in 1909 the term 'optic ataxia' has designated a disorder of coordination and accuracy of visually elicited hand movements not related to motor, somatosensory, visual acuity or visual field deficits. In the original case of Balint, which was related to bilateral infarction of the parieto-occipital junction, optic ataxia was associated with major impairments

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in visual attention. These included 'psychic paralysis of gaze' and neglect of left hemispace. Such disorders, however, could not account for optic ataxia, which only affected the right hand of the patient. Balint suggested that the hand motor area lacked access to visual information from the visual cortex. He conceived optic ataxia as the result of defective control of movement by vision and proposed that term as an analogy to tabetic ataxia. Indeed, his patient could perform body-orientated movements correctly, compensating for his deficit by using somatosensory cues in the same way tabetic patients compensate for their defective muscle position sense with vision.

Although subsequent descriptions of bilateral parieto-occipital syndromes have often been referred to as 'Balint's syndrome', the reaching disorders encountered have rarely taken the specific aspect observed in the original case. Apart from a few exceptions (Hécaen and Ajuriaguerra, 1954; Guard *et al.*, 1984), they have affected both hands and cannot clearly be dissociated from oculomotor or perceptual impairment. In fact, most of these bilateral syndromes are more reminiscent of the 'visual disorientation' of Holmes (1918). In this situation there are major oculomotor and visual space perceptive disorders which are thought to be directly responsible for the inaccurate visuomotor behaviour shown by these patients, either in reaching for objects or in avoiding obstacles when walking (e.g., Godwin-Austen, 1965; Michel *et al.*, 1965; Allison *et al.*, 1969; Kase *et al.*, 1977). The first published cases of misreaching following unilateral damage to the posterior parietal region were interpreted within a similar conceptual framework. Visual disorientation was thought to be restricted to 1 hemifield in those cases (Riddoch, 1935; Brain, 1941; Cole *et al.*, 1962).

Optic ataxia has only recently been recognized as a specific entity which may occur without perceptual, oculomotor or even visual attention disorders. Garcin *et al.* (1967) were the first to report that this symptom could appear in isolation. In their case, as in most similar ones reported later, optic ataxia resulted from a unilateral lesion centred on the posterior parietal region (Rondot and Recondo, 1974; Tzavaras and Masure, 1976; Rondot *et al.*, 1977; Levine *et al.*, 1978; Auerbach and Alexander, 1981; Ferro *et al.*, 1983; Ferro, 1984), although it was sometimes observed following bilateral lesions (Boller *et al.*, 1975; Damasio and Benton, 1979; Denes *et al.*, 1982). Typically patients are impaired in reaching with either hand for objects located in the visual hemifield contralateral to the lesion. However, other variations of this basic deficit have been encountered. In particular, misreaching may affect only 1 hand within 1 hemifield (Castaigne *et al.*, 1975; Rondot *et al.*, 1977), a symptom that can be neither a pure motor nor a pure perceptual disorder. Such observations as well as those reported in the present paper support the view that optic ataxia results from a specific visuomotor disruption, a notion that could still be deduced from Balint's case report.

Interest in optic ataxia has increased substantially in recent years with the development of experimental models of this symptom in the monkey. Optic ataxia has been viewed either as a visuomotor disconnection, equivalent to that performed by a leucotomy at the occipitoparietal junction (Haaxma and Kuypers, 1974) or as a loss of the posterior parietal neurons to which high order sensory association and motor initiation functions have been ascribed (Hyvärinen and Poranen, 1974; Mountcastle *et al.*, 1975; Lynch, 1980). Although lesions of the posterior parietal region result essentially in similar effects in man and in monkey, some discrepancies have also been noted between the two. These raise new questions with respect to optic ataxia. The disorder has mostly been described as a misreaching, that is, a directional imprecision of the proximal component or hand transportation phase of prehensile movements. Little attention has been paid to the distal component, namely the shaping of the hand in anticipation of the grasp. In the monkey the latter is affected by posterior parietal lesions. These 2 components have been considered as motor outputs of 2 types of visuomotor mechanisms or channels that deal with different aspects of visual information (*see* review in Jeannerod and Biguer, 1982). Whether the posterior parietal cortex of primates is involved in the control of both types of mechanisms is questionable. More careful testing of parietal deficits in man may help to solve this problem. The second point which appears to differ in man and monkey is that in man the deficit is usually related to a visual field effect, so that patients misreach with either hand only in the contralesional visual field, while in the monkey the deficit is only related to a hand effect, that is, monkeys misreach with the contralesional hand only, independent of the location of the object in space. For several reasons, however, this appears to be an oversimplification. In particular, with more systematic examination of patients with parietal damage, optic ataxia can sometimes be ascribed also to a hand effect, as observed recently in a few cases (Tzavaras and Masure, 1976; Levine *et al.*, 1978; Perenin *et al.*, 1979; Auerbach and Alexander, 1981; Ferro, 1984), and as will be reported in several of the patients of the present study.

Despite its heuristic value, it is likely that the parallel with animal models would not account for all aspects of optic ataxia. In fact, it might be expected that the functional and anatomical asymmetry of the human brain, particularly in the parietal region (Critchley, 1953; Eidelberg and Galaburda, 1984), would leave its mark on optic ataxia. It is thus interesting to know if, as proposed first by Tzavaras and Masure (1976), some aspects of optic ataxia such as the prevalence of field or hand effects, would depend on the side of the lesion.

In the present paper we have studied 10 cases of 'pure' optic ataxia following unilateral lesions of the posterior parietal region. The distribution of the deficit at the proximal and distal segments as well as in the different hand-field combinations was analysed by means of video and film recordings. This study was aimed at answering the following questions. To what extent can one consider optic ataxia as a specific visuomotor disorder, independent of visual space perceptive deficits? Does optic ataxia affect both the proximal and the distal components of prehensile movements? Does it differ in any way according to the side of the lesion? Finally, are there areas more frequently involved within the parietal lobe?

Preliminary results concerning some of the cases of the present study have been reported previously (Vighetto, 1980; Perenin and Vighetto, 1983).

## CASE REPORTS

All 10 patients had optic ataxia as a prominent clinical finding, and showed little or no associated visual, proprioceptive or motor deficits. Functional complaints related to hand misreaching were expressed by 5 of these patients. In other cases, optic ataxia was revealed following a systematic search.

In each case, a thorough neuropsychological examination was undertaken, including Hécaen's battery for apraxia (Hécaen, 1968), as well as the same author's batteries for language, memory and perception. The clinical features will be summarized below (for further details, *see* Appendix). All the patients were mainly right-handed.

### *Lesions*

The topography of lesions was defined by CT scan in all 10 patients. Direct observation of the location of the lesion was also available in 3 patients, who underwent surgical removal of a tumour (Cases 2, 10) or abscess (Case 3). Apart from these, the lesions were of vascular origin (infarction in 6 cases, haematoma in 1). The lesions were strictly unilateral, located on the right in 3 cases (Cases 1-3) and on the left in 7 (Cases 4-10).

Several CT scans were performed in most patients. In vascular cases, delayed CTs were used for anatomical studies in order to ensure a better delimitation of the lesions and to eliminate associated oedema. In 6 patients, joining 8 mm brain slices at an approximate angulation of 20° above the canthomeatal line were provided. In 4 patients, high resolution CT scans were available, supplying 4 mm brain slices. The plane of section was selected in these 4 cases as parallel to the fronto-occipital line, in order to fit best the templates used for reconstructions. Reconstructions of the lesions, both in sagittal and horizontal planes, were performed in all but 2 patients. The 2 excluded cases were a left hemisphere infarct with a technically poor CT scan and a right hemisphere tumour with major infiltrating oedema. Sagittal reconstructions were projected onto lateral diagrams of the hemisphere, according to the method of Mazzocchi and Vignolo (1978). Mapping of individual lesions allowed a gross estimate of superficial and deep involvement with respect to the lobes and major sulci of the hemisphere. Superimposition of the individual maps resulted in a composite diagram of the left and right hemisphere lesions that could show possibly a common lesion site. Horizontal reconstructions were aimed at delimitating precisely for each case the extent of the lesions in terms of subregional parcellation. We used templates representing sections of the brain parallel to the fronto-occipital line (Talairach and Szikla, 1967; Tokunaga *et al.*, 1977). We focused on the 5 upper templates, the level of which was +24 to +59 mm above the fronto-occipital line. Abnormal images seen on CT scan were plotted onto the appropriate templates. This plotting was straightforward for the 4 cases with high resolution CT scan (Cases 3, 6, 7, 8), but necessarily more approximate for the 4 other cases. We made a parcellation of the posterior parietal region on the templates using major sulci as boundaries of each subregion. Particular attention was paid to the following structures: inferior parietal lobule (IPL) including supramarginal (SMG) and angular gyri (AG), superior parietal lobule (SPL) subdivided into the medial part or precuneus and the lateral part, cuneus, intraparietal sulcus (IPS), parieto-occipital sulcus (POS) and the deep intraparietal white matter (DIPWM). A three-point semiquantification scale was devised to evaluate the extent of the lesion for each subregion (0 = no lesion; + = mild to moderate; ++ = severe to subtotal).

Lateral diagrams (fig. 1A) showed that the lesion was variable in extent but constantly involved the posterior parietal region. The lesion was limited to that region in 5 cases, and extended rostrally in the 3 other cases, respectively in the precentral (Case 7), premotor (Cases 7, 9) and cingulate areas (Case 6). A composite diagram of the lesions (fig. 1B) showed that a central 'core' was common to all cases. This core was symmetric in both hemispheres, projecting grossly on the inferior part of the SPL and the superior part of the IPL.

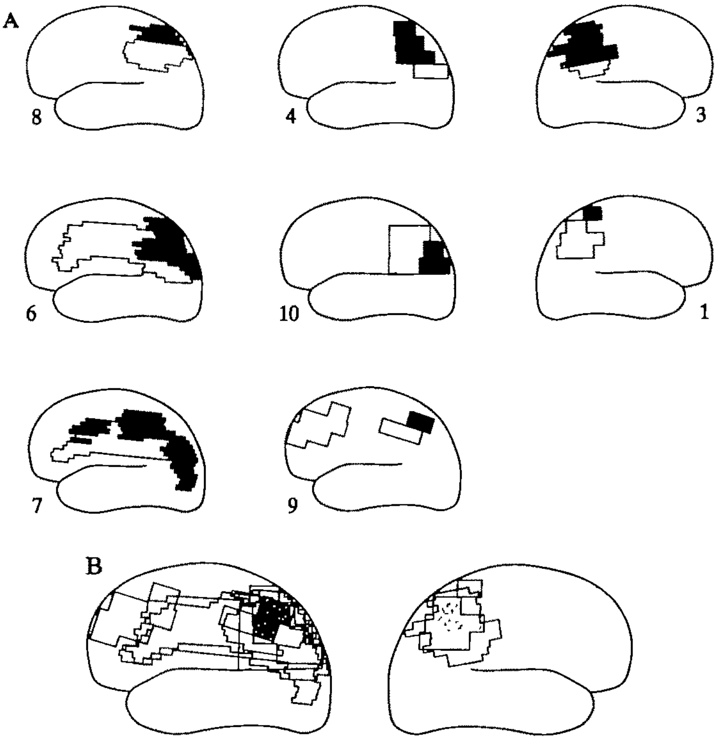

FIG. 1. Reconstruction of the lesions, drawn from CT scans, on lateral diagrams of the brain in 8 of the patients, identified by the case numbers. A, superficial and deep lesions are indicated, respectively, by hatched and uniform areas for each individual case. B, superimposition of the lesions in 6 left brain-damaged patients on the left, and of 2 right-damaged patients on the right. Lesions are centred on the upper part of the posterior parietal region on both diagrams. Grey area = 2 lesions; hatched area = 5 lesions, cross-hatched area = 6 lesions.

Horizontal reconstructions showed a constant involvement of both the cortex and the white matter of the posterior parietal lobe, the proportion of these two being variable from case to case. The white matter was almost spared only in Cases 1 and 4. Cerebral subregions involved by the lesions were the AG, the SPL, the IPS and the DIPWM. The IPS was involved in each case, SPL in all but 2 cases, IPL in 5 cases. Table 1 summarizes the data. Fig. 2 illustrates horizontal reconstruction for 3 of the patients.

Three groups of the patients could be recognized on anatomical grounds. Group I (n = 3: Cases 1, 8, 9) was characterized by a medial lesion, involving primarily the SPL, especially its medial aspect, the adjacent white matter and a part of the IPS. Group II (n = 3: Cases 4, 7, 10) was defined by a lateral lesion. There was a constant involvement of the IPS and the IPL, chiefly of the AG, and a more variable involvement of the SPL, then limited to its lateral part. Group III (n = 2: Cases 3, 6) represented a global lesion, adding lesions of groups I and II to a great part of the DIPWM.

### *Vision*

Visual acuity was normal or nearly so in all 10 patients. When tested with either the confrontation technique or the Tubingen perimeter with a large and bright spot (116 min, 318 cd/m$^2$) the visual field also appeared normal except in Case 10 who showed a right inferior quadrantanopia (fig. 3C). However, when small (10 min) and dim (< 10.2 cd/m$^2$) stimuli were used, some shrinkage of the visual field contralateral to the lesion could sometimes be observed with a corresponding decrease in contrast sensitivity on profile perimetry (Cases 1–4, 8; *see* fig. 3B for an illustration). In the remaining cases, even such precise perimetric conditions did not disclose any visual field defect (fig. 3A).

TABLE 1 LOCALIZATION OF LESIONS IN THE DIFFERENT SUBDIVISIONS OF THE POSTERIOR PARIETAL LOBE

| | | *Parietal subregions* | | | | | |
|---|---|---|---|---|---|---|---|
| | | *IPL* | | *SPL* | | *IPS* | *DIPWM* |
| | *Cases* | *SMG* | *AG* | *Medial* | *Lateral* | | |
| Right | 1 | 0 | 0 | ++ | + | + | 0 |
| | 3 | + | + | + | 0 | ++ | ++ |
| Left | 4 | 0 | + | 0 | 0 | + | 0 |
| | 6 | + | ++ | ++ | ++ | ++ | ++ |
| | 7 | + | + | 0 | 0 | ++ | + |
| | 8 | 0 | 0 | ++ | 0 | + | ++ |
| | 9 | 0 | 0 | + | 0 | + | + |
| | 10 | 0 | + | 0 | + | + | + |

IPL = inferior parietal lobule; SPL = superior parietal lobule; IPS = intraparietal sulcus; DIPWM = deep intraparietal white matter; SMG = supramarginal gyrus; AG = angular gyrus.

Patients showing a perimetric shrinkage for small stimuli often found that contours and colours were weaker in the contralesional than in the ipsilesional field. Furthermore, some visual attention disorders could be observed in the contralesional field in 4 of them (Cases 1, 2, 4, 8). When they were presented with several objects in that hemifield they often failed to detect the more peripheral one, although this could be seen when presented individually. This was not observed in the ipsilesional field. In addition, no extinction or only a fugitive one (Case 8) was found in a rivalry condition between the two hemifields. Patients having a fairly normal visual field did not show any extinction phenomena. In addition, they could recognize objects and colours equally well in both hemifields.

Visual space perception always appeared normal on clinical examination. All patients could give a correct (or nearly correct) verbal estimate of the distance or the relative position of objects within each hemifield. All of them could also judge if the orientation of 2 rods, each presented within 1 hemifield, was the same or different. However, in a tachistoscopic study performed in 5 patients and which will be described further, some errors were observed when single dots or lines were presented briefly.

### *Eye movements*

None of the 10 patients exhibited any gross oculomotor impairment. Their eye movements were full in all directions and they could shift their gaze at objects located anywhere in their visual field,

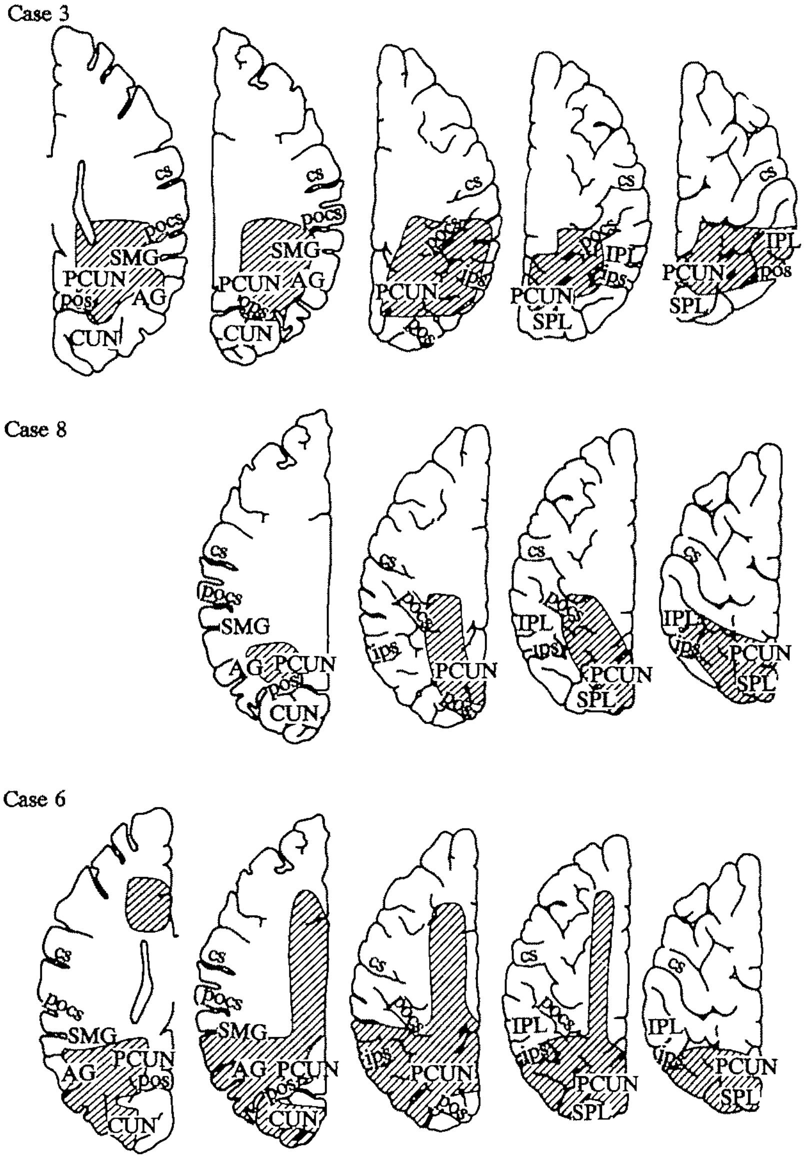

FIG. 2. Three examples of horizontal reconstruction of the lesions. The templates represent sections of the brain parallel to the fronto-occipital line, respectively, at 24 to 59 mm above this line. cs = central sulcus; ips = intraparietal sulcus; pocs = postcentral sulcus; pos = parieto-occipital sulcus AG = angular gyrus, CUN = cuneus, IPL = inferior parietal lobule; PCUN = precuneus, SMG = supramarginal gyrus; SPL = superior parietal lobule.

but when recorded by EOG during a pointing experiment performed in 4 patients (Cases 2, 3, 6, 7), visually elicited saccades did not always appear normal. Their latencies could be increased and they could show a staircase pattern, mostly when directed at targets located in the field contralateral to the lesion. This will be described in further detail elsewhere.

### *Somaesthesia*

Somatosensory sensations were largely spared. Only a few errors of position sense were observed on fingers contralateral to the lesion in Cases 1, 3, 5 and 7. When required to seize either thumb passively moved by the examiner, the patients had no difficulty in reaching for them with eyes open or closed. They performed well-adapted and rapid movements. In 2 patients (Cases 5, 7) tactile extinction occurred on the hand contralateral to the lesion when both hands were stimulated at the same time. Stereognosis was normal except in Cases 4 and 7 who made a few errors in identifying three-dimensional shapes with the right hand, and in Case 9 who showed a pure form of astereognosis, that is, without elementary tactile or position sense impairment. Somatosensory evoked potentials were recorded in 4 cases using the paradigm of Mauguière *et al.* (1983). Parietal responses were normal in Case 8 and only attenuated in their latest component in Cases 1, 2 and 9.

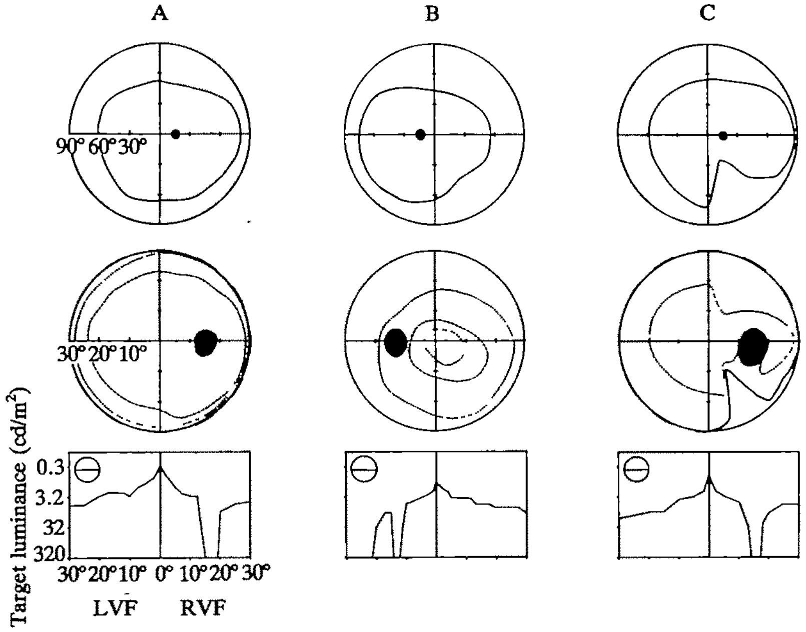

FIG. 3. The three different types of visual field recorded with the Tubingen perimeter Only the monocular field of the contralesional eye is figured here. *Upper part*: 90° dynamic perimetry using a 116 min of arc diameter, 318 cd/m² luminance, test spot. *Middle part*: 30° dynamic perimetry using test spots of 10 min of arc diameter, 318 cd/m² (continuous lines), 10.2 cd/m² (dotted lines), 3 18 cd/m² (broken lines) and 2 cd/m² (circles) luminance. *Lower part*. 30° static perimetry using a 10 min of arc diameter spot, along the horizontal meridian. LVF and RVF = left and right visual fields. A, normal visual field (*Case 7*), B, concentric shrinkage of the contralesional field only observed on the 30° dynamic and static tests (*Case 1*), C, contralesional inferior quadrantanopia (*Case 10*). Background luminance is 3.18 cd/m² in all testing conditions.

### *Motor functions*

Elementary motor capacities were on the whole unaltered. Apart from a slight weakness of the right thumb-index grip in Cases 4 and 7, muscular strength was normal and symmetric in all cases. However, in half (Cases 1, 3, 4, 5, 7), alternating and repetitive finger movements, such as strumming and tapping, were slower on the contralesional than on the ipsilesional side. Most of the patients (Cases 1, 4–9) showed, to various degrees, hypokinesia of the arm contralateral to the lesion. This appeared as a lack of arm swing during walking or as an absence of spontaneous use of the limb during everyday manipulative tasks or during examination for apraxia. In the most severe cases, who had a left hemisphere lesion (5, 6, 8, 9), the disorder resulted in a loss of the right hand preference, most gestures being performed or initiated by the left hand. In several cases (5, 6, 9) there was also an abnormal posture at rest of the contralesional arm, which remained half-flexed and pressed to the body. Finally, gestures were often altered by various degrees of apraxia in the patients with left-sided lesions (*see* below).

### *Neuropsychological symptoms*

Neuropsychological symptoms related to parietal lesions were observed to a varying extent in 9 of the 10 patients. The most frequent were different types of apraxia. Mild to severe ideomotor and ideational apraxia were present in 4 of the left-damaged cases (4–7). Case 5 mostly showed slow, clumsy and approximative gestures when using his right hand, rather than a true apraxia. Similar flaws were also observed in the movements of the right hand of the 3 other patients but they were part of a genuine bilateral ideomotor and ideational apraxia with amorphous, perseverative or sometimes noninitiated gestures. Constructional apraxia was shown by the 3 right-damaged patients and in 4 of the left-damaged cases (4–6, 8).

Gerstmann's syndrome was also a rather frequent symptom, being found in 4 of the left lesion group (6–9). Body schema was altered only in Case 6 who showed some degree of autotopagnosia. Hemispatial neglect was searched for with particular care in each patient by means of the following tests: line bisection, Albert's test of crossing-out line segments, counting objects or people, reading, writing and drawing a daisy and a clock. This symptom showed a remarkably low incidence as it only occurred in 2 cases (6, 8). In writing and drawing these 2 patients only used the leftmost part of the sheet of paper, although they performed correctly in the other tasks such as crossing-out line segments. Finally, Cases 2 and 3 showed some difficulties in route finding on a map. However, none of them showed any topographical disorientation. No signs of aphasia or memory deficit, or of visual agnosia, were observed in any of the patients.

## METHODS

Optic ataxia was analysed systematically by means of video and 16 mm film recordings in each patient. This was performed in 2 different situations intended to quantify the proximal and the distal deficits, reaching for an object and orientating the hand in a slit. In addition, visual space perception was further investigated tachistoscopically in 5 of the patients. Each of these tests was also carried out in a control group of at least 5 normal subjects. In the patients the data were always collected more than 3 weeks following the acute phase of the illness (infarct or operation for tumour), i.e., when the lesions had mostly stabilized and cerebral oedema resorbed. Thus the first series of tests were performed at 3 to 5 weeks postonset in 5 patients (Cases 1, 2, 6–8) and at 4 to 17 months in the others. The time course of optic ataxia could also be followed in 8 cases and formal testing performed again, in some of them, up to several years following illness onset.

### *Visual space perception*

The capacities to discriminate dot position and line orientation in either hemifield were investigated in a paradigm similar to that of previous studies (e.g., Kimura, 1969; Fontenot and Benton, 1972). The subject was seated at 57 cm from a uniform screen and required to fixate a small hole at its centre, through which the exàminer could control eye fixation. Stimuli were flashed singly for 200 ms in blocks of 25 and 30 trials per hemifield, both for position and orientation tests. Each test started with the ipsilesional field. In the position perception test, stimuli consisted of black dots of 1.5° diameter which could appear at 10, 15, 25, 35 or 45° from the fixation point. In the orientation perception test, stimuli were black lines of 15° length orientated at 0, 30, 60, 90, 120 or 150° with respect to horizontal and always centred at 27.5° from the fixation pont. After each trial the subject had to indicate verbally, using a multiple choice card, the number corresponding to the stimulus just flashed.

### *Reaching for an object*

Reaching movements were filmed by having in each case one camera placed in front of the subject so as to capture the whole hand transportation phase as well as eye behaviour. In some cases a second camera was also placed laterally in order to provide a simultaneous sagittal view of hand reaching. Three main conditions were used. In condition 1, the subject had to fixate the camera lens. He was asked to reach and grasp as quickly and accurately as possible an object (a big pencil) that was presented by the experimenter placed behind him at various locations successively in the ipsilesional hemifield, in the central field and then in the contralesional hemifield. First the hand ipsilateral and then contralateral to the lesion was tested. At least 10 trials were performed for each hand-field combination. In condition 2, 2 objects (pencils) were presented simultaneously, one in each hemifield and the subject was required to reach for them both at the same time while keeping the eyes fixated on the camera lens. In condition 3, only 1 object was presented but instead of fixating the camera lens the subject had to orientate eyes and head towards the object while reaching for it.

### *Orientation of the hand*

Hand orientation was studied with a simplified version of the test used by Haaxma and Kuypers (1974) in the monkey. In our version of the test the target was a white disc with an oval hole through which the extended hand had to pass. As in the reaching situation the different hand-field combinations were investigated systematically, but for this test the disc remained at the same place during a given hand-field session: at arm's length and 30 cm left or right from the midline or on the midline. Only the orientation of the main axis of the hole (horizontal, vertical and both 45° obliques) changed randomly from trial to trial. The disc was placed on a table which also served to standardize the starting point of the hand, on the midline and near to the body. A minimum of 10 trials were carried out for each hand-field combination. The whole arm and hand movement was always filmed through a posterior oblique view of the medial side of the limb; in some cases a frontal view of the disc was also taken with a second camera.

In this study, as will be seen below, accuracy has been analysed mainly in terms of the distribution of normal and missed responses across the different hand-field combinations. The possibility of using frame by frame (every 25 ms) viewing of the video tapes and films always clearly revealed missed responses, i.e., grasping in the air in the first test and erroneous orientation of the hand when approaching the disc in the second test. Over or underestimation of the target both in direction and distance was noted in the reaching test. Furthermore in the hand orientation test the amount of orientation errors was also estimated. Precise measurements of accuracy in a pointing task will be reported in a subsequent paper.

## RESULTS

### *Visual space perception*

Considered as a group, the patients who underwent the tests of position and orientation perception showed a greater mean number of errors in either test and either hemifield than the control group (t > 3.3, df = 27, $P < 0.05$). However, in the field ipsilateral to the lesion, individual scores for each patient, except Case 3, fell nearly into the control range in both tests. The same was not true in the visual field contralateral to the lesion, where individual scores exceeded the control range in 4 patients (Cases 3, 6, 7, 10) (Table 2).

TABLE 2. NUMBER OF ERRORS IN THE TESTS OF POSITION AND ORIENTATION PERCEPTION

| | *Position* (*n* = 25) | | *Orientation* (*n* = 30) | |
|---|---|---|---|---|
| *Controls* (*n* = 6) | *LVF* | *RVF* | *LVF* | *RVF* |
| *Mean* | 1.58±2.02 | 1.83±1.53 | 1.42±1.62 | 1.16±1.53 |
| *Range* | 0–6 | 0–4 | 0–5 | 0–5 |
| *Case* | *Ipsilesional* | *Contralesional* | *Ipsilesional* | *Contralesional* |
| 3 | 10 | 12 | 11 | 13 |
| 6 | 6 | 9 | 8 | 7 |
| 7 | 4 | 15 | 2 | 13 |
| 8 | 5 | 6 | 6 | 6 |
| 10 | 5 | 11 | 5 | 13 |

LVF, RVF = left and right visual fields Ipsi- and contralesional referred to the visual fields ipsilateral and contralateral to the lesion, respectively.

In the majority of cases, errors were of the same type as those encountered in the controls. They were 'proximity' errors, 2 neighbouring stimuli being confounded. Thus in the position test, errors almost never exceeded 10°. There was a trend to overestimate the eccentricity of near targets (up to the 25° target) and to underestimate that of distant targets. A similar 'proximity' effect was also observed in the orientation test, but errors almost only interested oblique stimuli. Thus the majority of errors were seen for stimuli oriented at 30° and 150° from horizontal which were perceived more vertically, that is, at 60° and 120°, respectively. However, in Case 3 with a right-sided lesion, another type of error also occurred which consisted of mirror-inverted responses to oblique stimuli (e.g., 30° instead of 150°, 60° instead of 120°, and the reverse). This was observed both in the contralesional and the ipsilesional visual field.

### *The proximal deficit of optic ataxia*

The proximal deficit was mainly studied and quantified in reaching tasks, with attention being focused on the arm projection component. Responses could be classified into 3 categories: 'normal', in which the subject reached and grasped the object directly; 'corrected', in which the subject initially missed the target by a variable amount and then corrected; and 'noncorrected' in which the subject missed the target and did not correct the error except when by chance his hand hit the object.

*Condition 1.* Results obtained in this condition (reaching for a single object while fixating the camera lens), are represented in fig. 4. This shows the distribution of the spatial errors (corrected and noncorrected) in each hand-field combination for each patient and for the control group. When the 2 lesion groups of patients were compared with the control group, consistent similarities or divergences (with a 0.05 level of significance on the t test) were observed depending on the different combinations, despite a few individual disparities within patient groups.

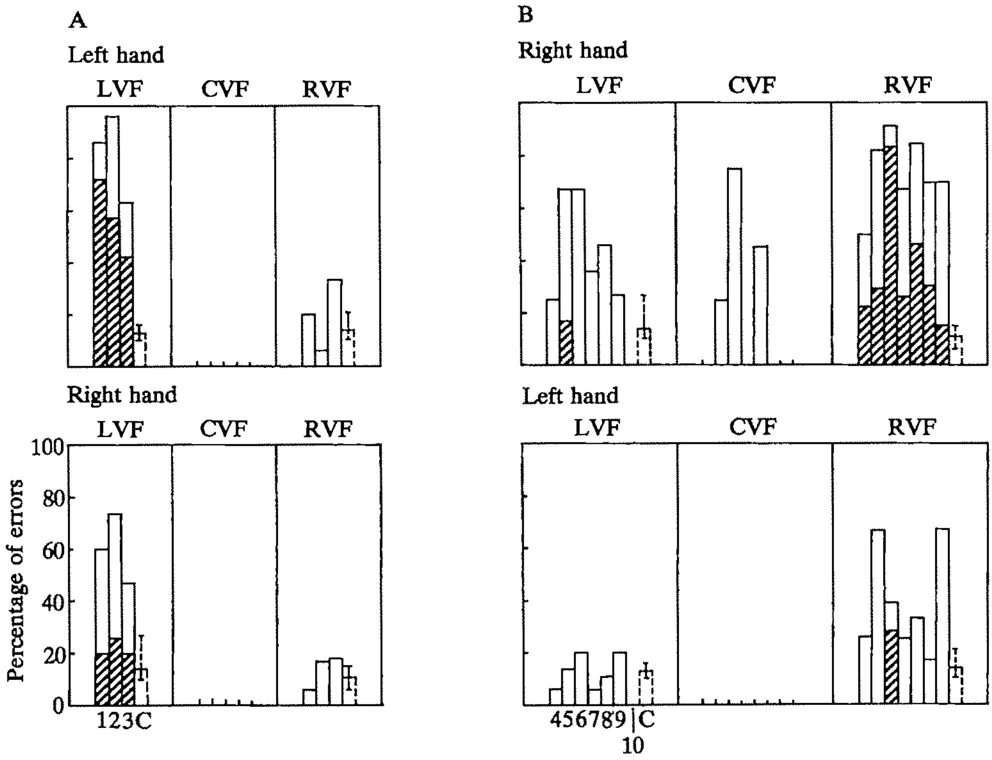

FIG. 4. Distribution of the spatial errors across the different hand-field combinations for each right-damaged (A) and each left-damaged (B) patient, and for the control group (C) during reaching at a visual object. The number of errors is given as the percentage of the total number of trials for each combination and each subject. White bars = corrected errors; hatched bars = noncorrected errors. LVF = left visual field; CVF = central visual field; RVF = right visual field. Note that in both groups of patients there is a 'visual field effect' (i.e., errors with both hands in the field contralateral to the lesion). In the left-damaged group (Case 10 excepted) there is an additional 'hand effect' (i.e., errors with the right hand not only in the right hemifield but also in the left hemifield and in 3 patients also in the central field).

Some findings appeared common to nearly all patients. Reaching with the ipsilesional hand in the ipsilesional field and in the central field was always similar to that of normal controls. In most trials the object could be grasped after a rapid and precise projection movement of the arm. There were only few errors (never exceeding 20%) of small amplitude, which always were corrected in the ipsilesional field. The maximum impairment occurred for reaching with the hand in the visual field contralateral to the lesion. High percentages of reaches with spatial errors were observed in this combination (from 50% in Case 4 up to 96% in Case 2), including many noncorrected errors (from 15% in Case 10 up to 83% in Case 6). Thus after a rather slow and hesitating movement of the arm, the patients often failed to grasp the object. Finally, except in Case 9, the ipsilesional hand was also impaired in the contralesional field, although to a lesser extent. Most errors observed in this combination were corrected. Such a 'visual field effect' (both hands affected in the visual field contralateral to the lesion) was a nearly constant finding, the only one exception being Case 9 who behaved as for the normals with the ipsilesional hand.

Differences in the distribution of errors were observed between right and left-damaged patients. The proportion of corrected errors was less in the former than in the latter (Case 6 excepted). Moreover, all left-damaged patients except Case 10 showed in addition to a visual field effect, a marked 'hand effect'. The right hand (contralateral to the lesion) misreached the object, not only in the right field but also in the left field (ipsilateral to the lesion). In 3 of these patients, the right hand was also affected in the central field. Errors were mostly of the corrected type. The hand effect observed in the left-damaged patients appeared as important (or in some cases, even more important) than the field effect, when error percentages of the right hand in the left field were compared with those of the left hand in the right field ($t = 0.07$, n.s., for the whole group). In the right-damaged patients, such a hand effect was absent (Cases 1, 2) or only very slight (Case 3).

Careful examination of the direction of spatial errors with respect to target did not disclose any clear directional bias in any of the patients. Although reaching was more often hypermetric along the sagittal plane, no systematic directional effect could be observed along the frontal plane. In several patients, in fact, reaching movements tended to be hypermetric for near targets and hypometric for far targets. A sweeping strategy was used in many trials. Error amplitude could only be approximately evaluated in this study. It appeared to range from a few degrees up to more than 30° or 40°. The largest errors always occurred with the contralesional hand in the contralesional visual field.

*Condition 2.* This condition, scores of which are shown in Table 3, was aimed at determining the influence of simultaneous reaching movements of the ipsilesional hand on those performed by the contralesional hand and to check again the prevalence of the field or hand effect. In the 'uncrossed reaching' subcondition, when each hand had to reach the object on the same side, the performances were similar to those of the controls in the ipsilesional hemifield but they were strongly impaired on the contralesional hemifield. In this combination most of the patients performed even worse than in reaching for a single object. They made fewer no-error responses and more noncorrected errors, up to 100% in Case 6. In a few trials (mostly in Case 6) patients did not even initiate any displacement of the arm. In the absence of visual extinction this might be interpreted as a motor extinction phenomenon, related to contralesional limb hypokinesia. In some cases the contralesional hand appeared to follow the trajectory of the ipsilesional hand towards the same object but, in most, misreaching with the contralesional hand was directed at a symmetric position to that occupied by the object in the ipsilesional field. In the 'crossed reaching' subcondition, when each hand had to reach the object on the other side, a test performed in 6 of the patients, the prevalence of the field or hand effect appeared more clearly than in the condition of reaching for a single object. It conformed to responses observed in the latter

TABLE 3 REACHING FOR TWO OBJECTS SIMULTANEOUSLY

| | *Uncrossed reaching* | | | | | | *Crossed reaching* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *LH–LVF* | | | *RH–RVF* | | | *LH–RVF* | | | *RH–LVF* | | |
| | *NOE* | *CE* | *UE* | *NOE* | *CE* | *UE* | *NOE* | *CE* | *UE* | *NOE* | *CE* | *UE* |
| Controls | 96 | 4 | | 96 | 4 | | 97 | 3 | | 91 | 9 | |
| Right-sided lesion cases | | | | | | | | | | | | |
| 1 | 11 | | 89 | 100 | | | | | | | | |
| 2 | 38 | 19 | 43 | 100 | 0 | 0 | 73 | 27 | 0 | 0 | 36 | 64 |
| 3 (1) | 27 | 33 | 40 | 93 | 0 | 7 | | | | | | |
| (2) | 14 | 36 | 50 | 100 | 0 | 0 | | 100 | | 100 | | |
| (3) | 23.5 | 23.5 | 53 | 94 | 6 | | | | | | | |
| Left-sided lesion cases | | | | | | | | | | | | |
| 4 | 97 | 0 | 3 | 48 | 28 | 24 | | | | | | |
| 5 | 100 | 0 | 0 | 25 | 50 | 25 | | | | | | |
| 6 (1) | 100 | 0 | 0 | 0 | 0 | 100 | | | | | | |
| (2) | 95.5 | 4.5 | | 23 | 50 | 27 | 86 | 14 | | 71 | 29 | |
| (3) | 100 | | | 11 | 56 | 33 | | | | | | |
| 7 (1) | 100 | 0 | 0 | 14 | 36 | 50 | 33 | 67 | | 17 | 83 | |
| (2) | 100 | | | 50 | 31 | 19 | 100 | | | 25 | 75 | |
| 8 (1) | 91 | 9 | | 4.5 | 50 | 45.5 | 83 | 17 | | | 100 | |
| (2) | 89 | 11 | | 28 | 55 | 17 | 100 | | | 33 | 50 | 17 |
| 9 | 92 | 8 | | 31 | 69 | | | | | | | |
| 10 | 96 | 4 | | 26 | 65 | 9 | 46 | 46 | 8 | 77 | 23 | |

* Percentages of responses with no errors (NOE), corrected (CE) and uncorrected errors (UE), in the different hand-field combinations. LH, RH = left and right hands. LVF, RVF = left and right visual fields. (1), (2), (3) = first, second and third series of tests.

except in Case 3, whose errors were more related to the hand than to the field contralateral to the lesion.

*Condition 3.* As shown on Table 4, when subjects had to orient their eyes and head towards the object, which was presented singly, reaching improved dramatically in all cases. As in the controls, errors could no longer be detected in most of the patients. In the other cases a few corrected errors of small amplitude occurred with the contralesional hand. Normal responses always approached or exceeded 90% except in Case 6 where it was only of 33% and 37.5% in the left and right hemispaces, respectively.

## *The distal deficit of optic ataxia*

The distal deficit was mainly analysed in the hand orientation test which was carried out in 7 of the patients. The task of passing the hand through the hole of the disc was accomplished by all of them, although often slowly and awkwardly.

TABLE 4 REACHING WITH EYE-HEAD ORIENTATION TOWARD THE OBJECT (PERCENTAGE CORRECT)

| | *LVS* | | *CVS* | | *RVS* | |
|---|---|---|---|---|---|---|
| | *LH* | *RH* | *LH* | *RH* | *LH* | *RH* |
| Controls | 100 | 100 | 100 | 100 | 100 | 100 |
| Right-sided lesion cases | | | | | | |
| 1 | 89 | 100 | | | | 100 |
| 2 | 100 | 100 | 100 | 100 | 100 | 100 |
| 3 | 89.5 | 100 | 100 | 100 | 93 | 100 |
| Left-sided lesion cases | | | | | | |
| 4 | | | | | | 100 |
| 5 | 100 | 100 | | | | |
| 6 | 100 | 37.5 | 100 | 83 | 100 | 33 |
| 7 | 100 | 89 | 100 | 100 | 100 | 100 |
| 8 | 100 | 93 | 100 | 100 | 100 | 72 |
| 9 | 100 | 100 | 100 | 100 | 100 | 90 |
| 10 | 100 | 92 | 100 | 100 | 100 | 89.5 |

LVS, CVS, RVS = left, central and right visual spaces; LH = left hand, RH = right hand.

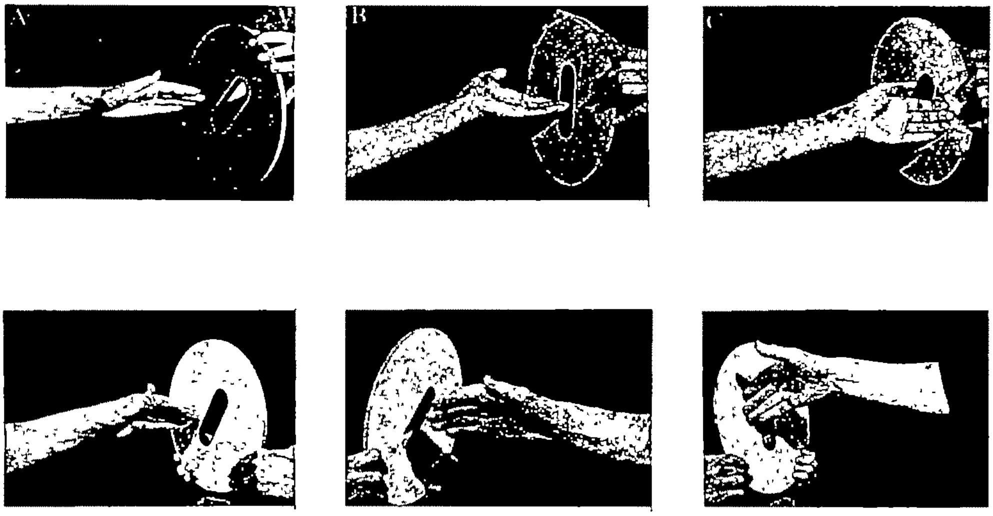

FIG. 5. The three different kinds of responses observed in the hand orientation test. A, normal response; B, orientation error; C, spatial error. *Upper part*: left hand of *Case 2* in the right hemifield (A) and in the left hemifield (B, C). *Lower part*: left hand of *Case 8* in the left hemifield (A) and right hand in the right hemifield (B, C).

As the hand approached the disc, both spatial and orientation errors could be observed (fig. 5). These 2 types of errors occurred either separately or, more often, together. Spatial errors were generally of small amplitude and always of the corrected type. This probably resulted from the fact that the target was large and always located at the same place for a given hand-field session. Hand orientation errors were observed in the right-damaged as well as the left-damaged patients. Their distribution shown in fig. 6 was very similar to that of the misreaching seen in fig. 4. For the right-damaged patients, orientation errors occurred only (Case 2) or mainly (Case 3) in the visual field contralateral to the lesion, whichever hand was used. In contrast, all left-damaged patients except Case 10 showed not only a field effect but a hand effect as well. Angular errors ranged from 45° to 90° in most cases, but a total inversion of the normal hand posture (corresponding to a 180° error) sometimes occurred (mainly in Case 4). The most common impairment consisted in the lack of any anticipatory orientation of the hand which remained horizontal from the starting position on the table up to contact with the disc, whichever orientation had the slit.

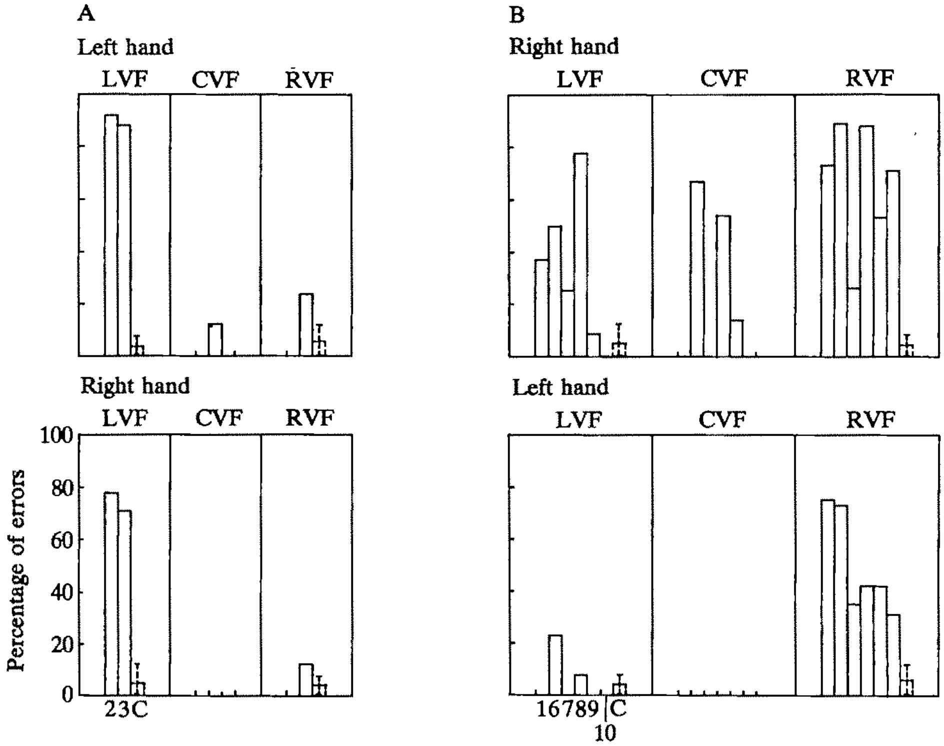

FIG. 6 Distribution of the orientation errors of the hand across the different hand-field combinations for 2 right-damaged (A) and 5 left-damaged (B) patients and for the control group (C) during the hand orientation test shown in fig. 5. LVF = left visual field; CVF = central visual field; RVF = right visual field. Visual field and hand effects are similar to those observed for spatial errors in the 2 groups of patients.

Absence of orientation or misorientation of the hand was not the only distal deficit. Frame by frame analysis disclosed in all patients and in both testing situations a failure of the ability to shape the hand with adequate finger postures

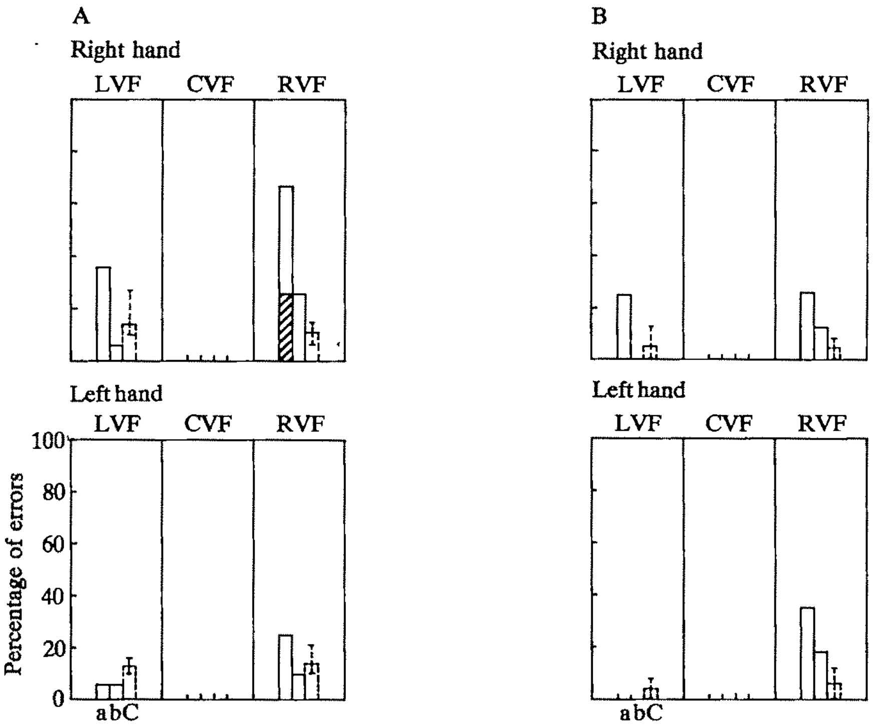

FIG. 7. Example of a nearly complete recovery of optic ataxia Performances of *Case 7* at 3 wks (a) and 6 yrs (b) postonset are shown as percentage of errors in the reaching (A) and hand orientation (B) tests, for the different hand-field combinations. Details otherwise as in legend for fig. 4

to conform to the target object. This defect had the same distribution across the different hand-field combinations as the spatial errors. In reaching for an object, a 'fanned' aspect of the hand was commonly observed, with fingers fully extended and spread out throughout the transportation phase. In addition, most of the left-damaged patients showed impairments with the right hand not observed in the right-damaged patients. Movements were generally more hesitant in grasping for the target. Totally unadapted motor behaviour was sometimes seen, mostly in those patients also having motor apraxia (Cases 4, 6, 7). For example, the hand could remain closed during its whole trajectory or could be moved into useless alternating prone and supine positions. In the hand orientation task some fingers remained flexed and could not be passed into the hole. Finally, the left-damaged patients often failed to use tactile cues to achieve the task when the right hand touched the target by chance, despite the absence of any significant tactile deficit.

### *Further insight into 'motor' aspects of optic ataxia*

The deficit of our patients did not only consist in an inaccuracy of the proximal and distal components of visually-elicited arm movements. As already mentioned, movements were often hesitant in reaching for an object; they were uncoordinated and 'ataxic', mostly when approaching the target. Moreover, the initial hand transportation movement (up to the end of the first deceleration) was much slower than normal. Systematic study of movement time during a pointing task will be reported in a subsequent paper; thus we will only indicate here ranges representative of hand transportation duration drawn from film analysis in the present reaching situation. The highest values, ranging from 850 to 1550 ms, were always observed in reaching with the hand in the visual field contralateral to the lesion while normal ranges of movement duration from 450 to 600 ms (i.e., similar to the controls) were found in the ipsilesional hand-field combination. It should be stressed, however, that slowing of the contralateral arm movements cannot be considered as truly 'motor' in nature. In fact it was not evenly distributed throughout the working field. Movements with this arm were either normal or less increased in duration in the ipsilesional hemifield. In addition, the ipsilesional arm was often slower in the contralesional field. Anomalies of speed, in fact, tended to have a similar distribution as did anomalies of accuracy. Another reason for excluding some basic motor disorder on the contralesional hand lies in observations recorded when targets other than visual were used. As already

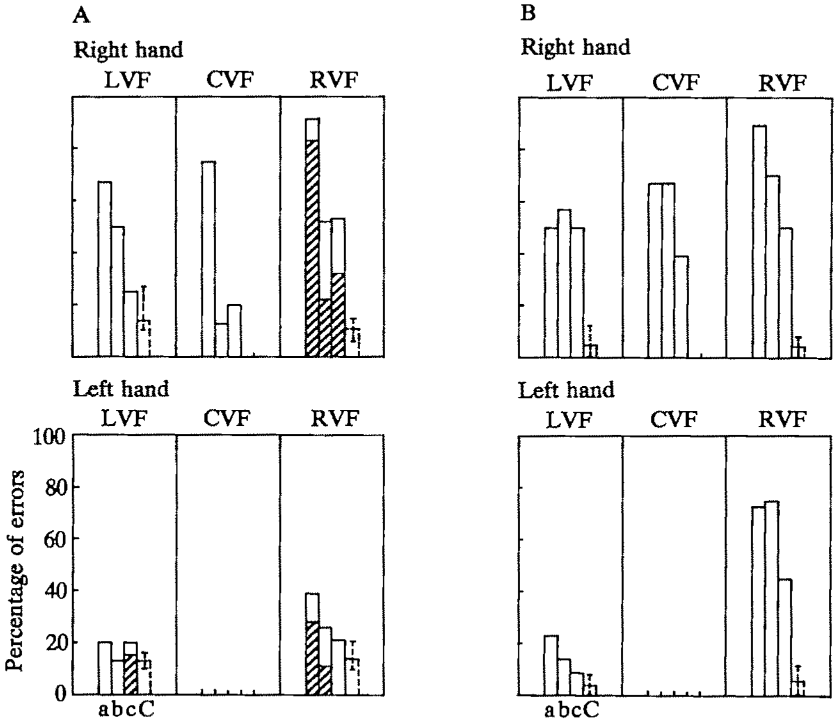

FIG. 8. Example of partial recovery from optic ataxia. Performances of *Case 6* at 1.5 months (a), 3.5 months (b) and 5 yrs (c) postonset are shown as percentage of errors in the reaching, (A) and hand-orientation (B) tests for the different hand-field combinations. Details otherwise as in legend for fig. 4.

mentioned all the patients could perform precise and rapid body orientated movements and reaching for either thumb. They also behaved as normals or nearly so when required to reach for or to point towards an auditory target (a small loudspeaker) located at various places in front of them, while keeping their eyes closed. Case 6 was an exception, showing systematic errors (towards the lesion side) and slower movements in pointing at auditory targets with his contralesional hand. Apart from this patient, movements of comparable amplitude and direction showed normal and similar durations in both hands, ranging between 600 and 700 ms and between 750 and 850 ms, respectively, for the kinaesthetic (thumb grasp) and auditory modalities.

### *Time-course*

Eight of the patients were further examined at various time intervals from illness onset, ranging from 3 months to 6 years. Four of them underwent only an informal examination, while in the other 4 (Cases 3, 6–8) errors were requantified, using the same paradigm. In 2 patients (Cases 1, 7) recovery from optic ataxia was almost complete, as shown in fig. 7 for Case 7. In both, however, the bimanual reaching condition appeared to reemphasize the deficit, as error percentages increased up to 50% in uncrossed reaching and 75% in crossed reaching. In the other 6 patients optic ataxia was still present even some years after its onset, although there was a general trend towards partial recovery, as shown in fig. 8 for Case 6.

## DISCUSSION

### *Specificity of optic ataxia*

The idea that optic ataxia would rely on a specific visuomotor disorder underlies several single case reports in the literature, starting with that of Balint (1909). Yet this idea has not received complete acceptance, probably due to the lack of systematic investigations. The results of the present study provide some clear arguments that support the specificity of the optic ataxia deficit.

They demonstrate, first, that optic ataxia may appear as a modality-specific symptom. Apart from Case 6 who showed some degree of 'auditory ataxia', there was in all patients a striking contrast between the marked incoordination, slowness and inaccuracy of visually-elicited hand movements and the normal (or nearly normal) pattern of movements directed at kinaesthetic or auditory targets. The latter modality has seldom been investigated in previous studies. In their 2 optic ataxia patients, Tzavaras and Masure (1976) observed that reaching for auditory targets was either normal or minimally affected. There have been more data recorded for the somaesthetic modality. Like Balint, several authors have contrasted the gross impairment of hand movements under visual guidance with the well coordinated, rapid and accurate pattern of movements directed at the body (Garcin *et al.*, 1967; Rondot *et al.*, 1977; Damasio and Benton, 1979). In a few cases, however, inaccuracy was observed in pointing at body parts, even in the absence of elementary somatosensory disorders (Levine *et al.*, 1978; Boller *et al.*, 1975).

Our results stress another aspect of the specificity of the optic ataxia deficit. This appears neither sensory nor motor in nature, but more probably related to a selective disruption at the junction of both domains. None of the patients showed any significant motor, proprioceptive, visual field or visual space perception disturbances. Although some constriction of the contralesional hemifield could be observed when small and dim stimuli were used and although the capacity to discriminate dot position and line orientation could be impaired, mostly in that hemifield when brief stimuli were presented, a direct link between these subtle deficits and optic ataxia cannot be envisaged. The first reason lies in the fact that they were not observed in all patients. Moreover, errors detected by the tachistoscopic study in 4 patients were much smaller than errors in reaching and hand orientation and did not show any correlation with them. On the other hand, such deficits could not account for the fact that, in many of our patients, optic ataxia was not only related to the contralesional visual half-field but also to the contralesional hand. Finally, a decisive argument for rejecting the dependence of perceptive disorders, even if very slight, on optic ataxia and for considering this symptom as a very specific one lies in the fact that it can affect only 1 hand within 1 hemifield. This pattern of deficit can be observed from illness onset (e.g., Case 3, Rondot *et al.*, 1977) or more often at a later stage of evolution (e.g., Case 1, Tzavaras and Masure, 1976; Cases 6, 7, present series). In this way, optic ataxia appears to differ from visual disorientation in 1 hemifield described in the past (Brain, 1941; Cole *et al.*, 1962). In contrast to this situation, perceptive disorders in patients with optic ataxia would only have an accessory character. They might result from marginal extension of the lesion to parietal subregions more involved in visual space perception and/or visual attention than those critically injured in optic ataxia.

### *Proximal and distal components of the deficit*

As observed in all our left and right-damaged patients, optic ataxia consists in both a proximal and a distal deficit of visually directed arm movements. Previous descriptions have mostly emphasized misreaching. Distal deficits, when mentioned, mainly involved independent finger movements during manipulation of the visual target (Damasio and Benton, 1979). Tzavaras and Masure (1976), however, used the same manipulandum as Haaxma and Kuypers (1974) and observed an absence of the anticipatory shaping of the thumb-index grip in a left-damaged patient but not in 1 with a right-sided lesion. In our series misorientation and misshaping of the hand occurred regardless of lesion side. This distal deficit was also found in another study on both a left and a right-damaged patient of the present series, mostly dealing with the kinematics of prehensile movements. In central vision, and mainly when view of the hand was prevented, these 2 patients (Cases 3, 9) grasped a small three-dimensional object with the palmar surface of the hand instead of with the finger tips (Jeannerod, 1986).

In the past 15 years there has been increasing support for the concept that prehension is subserved by 2 kinds of visuomotor mechanisms or channels. 'Space' and 'object' channels dealing, respectively, with the spatial location and shape of the objects, would pick up information each at a different level of the visual system (the midbrain and visual cortex levels, respectively, according to the 'two visual systems' hypothesis; Trevarthen, 1968; Schneider, 1969) and produce motor outputs on different arm segments, namely on the proximal and distal segments, respectively. Arguments in support of this theory, reviewed in Jeannerod and Biguer (1982) are mainly from developmental studies in human and monkey infants and from split-brain experiments, each showing a dissociation of the 2 components of prehension. Thus the proximal component matures much earlier after birth than the distal component. Moreover, as shown in split-brain monkeys, independent hand and finger movements are exclusively mediated by the contralateral corticomotoneuronal pyramidal pathway, whereas proximal motricity depends on both contralateral and ipsilateral corticospinal and subcorticospinal pathways (Brinkman and Kuypers, 1973).

In agreement with the latter results, interruption of the connections between visual cortex and the precentral motor area impairs the adjustment of finger posture to target more than other components of visually-directed arm movements. This was shown by Haaxma and Kuypers (1974) after a unilateral leucotomy at the parieto-occipital junction in split-brain monkeys. When the animals had to seize small pieces of food from narrow grooves, a task requiring a precise shaping of the fingers, they failed in using the contralesional hand. A similar disorder is observed after larger posterior parietal lesions including areas 5 and 7 (Lamotte and Acuña, 1978) or area 7 alone (Faugier-Grimaud *et al.*, 1978). However, such lesions impair both the directional precision of the arm movement and the postural adaptation of the hand and fingers on the contralesional side. In humans with lesions of the posterior parietal region, there is not yet evidences for a differential impairment of the proximal and distal components depending on the site, deep or superficial, of the lesions. Comparison with animal findings, however, indicates that lesions of the cortex achieve a much closer animal model of optic ataxia than that resulting from occipitofrontal disconnection.

Thus, in monkey and man, damage to the posterior parietal cortex should alter both visuomotor mechanisms involved in prehension. This fits with a number of experimental data, both anatomical and physiological. The posterior parietal cortex receives indirect visual information from the two visual systems. It is connected to the superior colliculus and to the pretectum via the pulvinar (Benevento and Fallon, 1975; Baleydier and Mauguière, 1977) and to the geniculostriate pathway via the prestriate cortex and dorsal thalamus (Jones and Powell, 1970; Mesulam *et al.*, 1977). In recent years, single cell recordings in posterior parietal cortex of the behaving monkey have disclosed several categories of cells whose properties are all compatible with a general function of this cortical zone in matching spatial relationships between the different body parts and the immediate surrounding space. It has been proposed that this part of the cortex would subserve high-order sensory integration and initiation of motor actions such as looking and reaching for objects (Mountcastle, 1978; Lynch, 1980; Hyvärinen, 1982). In particular, in areas 5 and 7 there is a significant proportion of cells which are specifically activated either in relation to arm reaching movements or during hand manipulation, sometimes for a given region of space, one more argument to favour these areas as being involved in both visuomotor mechanisms underlying prehension.

### *Different aspects of optic ataxia with regard to the side of the lesion*

As already mentioned, optic ataxia was first described as a visual field-related deficit as opposed to the hand-related deficit of the monkey. Interestingly, all early reports concerned right-damaged patients. In fact, as shown by a few previous cases and by the present study, optic ataxia may also be related to a hand effect. Moreover, the distribution of the deficit according to field or hand effects appears to depend on the side of the lesion. Thus, as confirmed in 3 of our patients, an isolated visual field effect would characterize optic ataxia resulting from a right-sided lesion. Associated field and hand effects, as seen in 6 of our patients and in 4 reported before (Tzavaras *et al.*, 1974; Tzavaras and Masure, 1976; Auerbach and Alexander, 1981; Ferro, 1984) appear to characterize optic ataxia resulting from a left-sided lesion. The only 2 exceptions, out of a total of 22 observations of optic ataxia with unilateral lesions (including the previously reported and the present cases), are our left-damaged Case 10 who failed to show any hand effect in the present testing condition, and a right-damaged patient reported by Levine *et al.* (1978) who exhibited a hand effect, but mostly when prevented from viewing his limb.

The difference which appears globally in the distribution of the deficit according to the side of the lesion suggests an asymmetry of functional organization between right and left parietal areas subserving visually-directed movements. This represents one more example of the well-documented functional asymmetry between the 2 hemispheres in man. Furthermore, the prevalence of the field or hand effect, depending on the side of the lesion, could be related to the different specialization of each hemisphere, and the posterior parietal lobes in particular, for visuospatial abilities and spatial attention on the right side and for motor functions on the left.

The dominance of the left hemisphere and in particular of the left posterior parietal lobe in motor programming has been known since the work of Liepmann (1908) on apraxia and subsequently confirmed by a number of studies (e.g., Wyke, 1971; Kimura and Archibald, 1974; Heilman, 1979). In our left-damaged patients, 4 out of 7 showed various degrees of apraxic disorder, ranging from severe bilateral ideomotor and ideational apraxia to milder 'preapraxic' impairments consisting of clumsiness and slowness of gestures. These disorders often predominated in the right arm. When they performed visually-elicited movements, the left-damaged patients, compared with the right-damaged ones, showed additional distal impairments in their contralesional arm which were more marked in cases with associated apraxia. In such cases apraxia and optic ataxia appear cumulative in their effects. Addition of a motor apraxia seems rather frequent in cases of optic ataxia resulting from left parietal lesions (*see also* Tzavaras *et al.*, 1974; Tzavaras and Masure, 1976). However, as seen in our series and in a few previously reported cases (Auerbach and Alexander, 1981; Ferro *et al.*, 1983; Ferro, 1984; *see also* Balint's case), it is not constant. Thus these 2 symptoms would have independent, although probably topographically close neural substrates.

Various degrees of 'limb hypokinesia' or 'motor neglect' (according to the terminologies of Heilman *et al.* (1983) and Laplane and Degos (1983) respectively) were observed in most of our patients, including all but 1 left-damaged and 1 right-damaged patient. In the former, the intensity of hypokinesia did not appear to be related to the associated apraxia, as in the 3 most hypokinetic cases (5, 6, 9), Case 9 was not apraxic. Although limb hypokinesia may well be observed in patients with lesions restricted to the contralateral posterior parietal cortex, as in Cases 1, 4 and 9, in agreement with findings in the monkey (Faugier-Grimaud *et al.*, 1978), it appears more severe when parts of the frontal association cortex are also damaged as in Cases 6 and 9.

Contrasting with the high incidence of motor neglect, spatial neglect was only observed in 2 cases of our series. In these 2 patients (Cases 6, 8), only a few signs of right hemispatial neglect were present. Data from the literature also suggest that optic ataxia and hemispatial neglect do not often occur together. Dissociation of these 2 types of disturbance of spatial orientation is reinforced by anatomical findings showing different lesion sites for each within the posterior parietal cortex (*see* below). These results indicate a double dissociation of function, eye-hand coordination and spatial attention being subserved by at least partially distinct neural entities.

### *Anatomical substrate*

Our CT scan data provide confirmatory evidence that optic ataxia occurs after lesions of the posterior parietal lobe. Some additional lesions may in fact be found in the frontal lobe (Hécaen and de Ajuriaguerra, 1954) or in the corpus callosum (Ferro *et al.*, 1983), but these are occasional findings which in our series are present, respectively, in 3 and 1 out of the 10 cases. Damage to the posterior parietal lobe always involved the cortex and in most cases the white matter too. With the limitations of anatomical inferences drawn from CT scan pictures kept in mind, we find that the IPS, the SPL and to a lesser degree the IPL—particularly the angular gyrus—are the most commonly injured cortical regions. The IPS is the only structure to be involved in each case, although to a variable degree. From there the lesion extends either to the SPL, in particular to the precuneus, or slightly less often to the upper part of the IPL, or sometimes to both lobules. We therefore argue that the neural structures contained in the IPS and adjacent medial SPL and upper IPL are critical for optic ataxia.

Few anatomical descriptions based either on necropsy findings or even on CT scans are available in the literature on optic ataxia after unilateral lesions. Levine *et al.* (1978) reported a case of an astrocytoma in the dorsomedial portion of the right posterior parietal lobe, limited to the precuneus and underlying white matter. The patient of Auerbach and Alexander (1981) had a small infarct in the left SPL that was thought to be confined to Brodmann's area 7 on CT scan. The anatomically verified case of Ferro *et al.* (1983) showed infarction extending from the occipital pole to the posterior parietal gyrus. The two lips of the calcarine fissure, the cuneus, the precuneus and subjacent white matter were involved, as well as the dorsal splenium and a part of the frontal lobe. However, the convolutions of the external face of the hemisphere, the fusiform gyrus and most of the lingual gyrus were spared. Ferro (1984) described a case of transient hand misreaching related to a small infarct involving area 7 in the left parietal cortex and the underlying white matter. Finally, Ratcliff and Davies-Jones (1972) found in a series of cases of missile wound injuries that patients who misreached in the contralateral field had lesions located in the upper part of the parietal lobe. A few cases with bilateral lesions are relevant to the discussion. In the patient of Damasio and Benton (1979), who had bilateral infarction after a hypoxic insult, CT scan showed a dorsolateral and rather symmetric hypodensity near the parieto-occipital junction that encompassed, in Brodmann's nomenclature, the anterior part of area 19, area 7 and possibly area 39, in addition to severe white matter damage. Guard *et al.* (1984) reported postmortem observations on a case with bilateral and asymmetric lesions of distinct nature. Lesions were almost only subcortical and the corpus callosum was intact. In the left hemisphere, a glioma occupied the white matter of the parietal lobe, mostly deep to the IPL, although its upper pole infiltrated the cortex of area 7. In the right hemisphere, the lesion, a haemorrhagic infarct, was more limited and almost entirely located in the precuneus. The anatomically verified case of Pierrot-Deseilligny *et al.* (1986) is of particular interest because of the limited size of the vascular lesion. The injury common to both sides was essentially limited to both banks of the IPS. In addition, the upper aspect of the angular gyrus and, to a lesser degree, part of the adjacent lateral SPL, were bilaterally although asymmetrically involved.

No particular attention has been given to the IPS in all these previous studies. However, taken together, the data are consistent with our own findings in suggesting that optic ataxia results from cortical and/or subcortical lesions encompassing the IPS and extending most often superiorly and medially into the precuneus.

In terms of cortical involvement, the convexity and medial SPL comprises a homogeneous cytoarchitectonic type, corresponding to Brodmann (1909) area 7, or PE according to the nomenclature of von Economo (1929). The IPL is formed by a different and less homogeneous cytoarchitectonic type, corresponding to Brodmann areas 40 and 39 or von Economo areas PF and PG. The recent cytoarchitectonic study of Eidelberg and Galaburda (1984) has shown that the cortex of the dorsal and the ventral bank of the IPS is of PE and PEG type, respectively, the latter being a regional variant of the former. It may therefore be suggested that lesions resulting in optic ataxia should involve neuronal populations belonging to PEG and PE cortices. Volumetric asymmetries with a rightward bias for area PEG, noted by the same authors, might underlie a functional asymmetry and could account for the different aspect of optic ataxia according to the side of the lesion.

Comparisons between man and monkey are biased due to the still disputed homology between the IPL and SPL in both species. In the monkey, the IPL appears critical for visuomotor functions. As already mentioned, cortical excisions limited to this lobule result in a deficit resembling human optic ataxia (Faugier-Grimaud *et al.*, 1978). Hand misreaching is, however, transient, even after bilateral lesions. Cooling of the SPL alone gives rise to a loss of kinaesthetic control of hand movement (Stein, 1978). A lesion that includes both SPL and IPL results in a more profound and enduring movement deficit (Lamotte and Acuña, 1978). However, it is still questionable whether this is due to a mass effect of the lesions or to involvement of some other critical subarea in IPS or SPL. It can tentatively be suggested that lesions of IPS and neighbouring cortex would represent a common denominator of parietal lesions that give rise to hand misreaching in both man and monkey.

Single cell recordings in the behaving monkey have shown some regional differentiation according to the different functional categories of cells in the posterior parietal cortex (Hyvärinen, 1982), although these would be largely overlapping (Lynch, 1980). In fact, little is known about the functional organization of this region. A subdivision into subareas and then into functional 'modules', each having their own input-output relationships, has been proposed on the basis of anatomical data (Mountcastle *et al.*, 1980). The cytoarchitectonic parcellation observed more recently in the posterior parietal lobe, as well as the specific pattern of connectivity of each cortical subarea (Pandya and Seltzer, 1982) provide support for this hypothesis.

We believe that pathological observations such as those reported in the present paper on optic ataxia as well as clinical CT scan correlations on hemispatial neglect reported elsewhere (Heilman *et al.*, 1983; Vallar and Perani, 1986) also represent strong arguments in favour of a functional partition within the posterior parietal cortex. These two symptoms most often occur independently and result from lesions at different sites, thus demonstrating a double dissociation of function. Using reconstruction of lesions from CT scan images, Vallar and Perani (1986) have shown that lesions responsible for hemispatial neglect were centred on the ventral IPL and the parieto-temporo-occipital junction. Using a similar method we found that lesions in our optic ataxia cases were located more dorsally and centred on the IPS and adjacent SPL. This represents a first step in understanding how specific aspects of spatially-oriented behaviour subserved by the posterior parietal cortex are functionally organized.

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## APPENDIX

*Case 1 (C.B)*

This 54-yr-old right-handed woman with a history of migraine presented in January 1976 with the clinical picture of subarachnoid haemorrhage Focal signs were present, consisting of a moderate left-sided sensory-motor deficit, a left hemiasomatognosia and complex visual hallucinations. Angiography showed no vascular malformation. However, both angiography and radionuclide scanning indicated an intracerebral haematoma in the right parieto-occipital convexity. Evolution was largely regressive over 3 wks. One month postonset, the patient was alert, attentive, with normal language and memory functions. Motor skills with the left hand were moderately impaired but muscle strength was symmetric. The left upper limb remained somewhat hypokinetic with a lack of spontaneous arm swing while walking A slight decrease in position sense in the fingers was noted, without sensory extinction or astereognosis. Visual acuity was 10/10 bilaterally. Perimetry showed a constriction of the left visual field only for the smaller isopters. Although object recognition and line orientation discrimination were preserved in both visual fields, some degree of hemiachromatopsia was present in the left visual field, as well as extinction of the leftmost object under single field presentation of two objects. However, there was no visual extinction under double field stimulation and no hemispatial neglect. Ocular movements were normal. A moderate constructional apraxia was found. Map orientation was fair. There was no limb apraxia, visual agnosia or disorder of body image.

Optic ataxia had improved 2 yrs later and was no longer detectable 8 yrs postonset A CT scan, performed in 1984, showed a hypodense lesion in the medial aspect of the right parieto-occipital junction.

*Case 2 (J.P.)*

This 34-yr-old right-handed woman began to have focal sensory-motor epilepsy in 1975. Seizures consisted of ascending paraesthesiae affecting the left side of her body followed by hemiasomatognosia and sometimes by tonic-clonic jerks with a secondary generalization. CT scan performed in 1977 showed an ill-defined lesion in the internal and posterior part of the right hemisphere close to the ventricular body. Surgery was delayed until April 1979. At this time, the lesion had enlarged on CT scan and the patient had symptoms of raised intracranial pressure. Preoperative neurological examination was normal. The neurosurgeon found infiltration of the tumour reaching the cortex of the right retrorolandic and posterior parietal region. Only partial removal was carried out and histology demonstrated an astrocytoma. Her postoperative course was uneventful. Our evaluation began 4 wks postsurgery The patient was alert, attentive and had no functional complaints. She had no disorder of language, memory, praxis, calculation or body image. No motor or sensory deficit was found. Visual acuity was 10/10 bilaterally. Perimetry showed a normal visual field when a bright and large spot was used but some constriction of the left visual field on the smaller isopters. Moreover, some perceptive and attentional disorders could be demonstrated in this hemifield. Although there was no visual extinction in a double field presentation, it could be shown that the patient 'extinguished' the leftmost located object or colour when 2 items were simultaneously presented in the left hemifield. Estimation of distances was slightly misevaluated in that field but relative localization between objects and line orientation discrimination were good in both hemifields. There was no evidence of hemispatial neglect. Stereopsis was moderately impaired on the Titmus test. Ocular motility was normal and optokinetic nystagmus (OKN) was symmetric. Severe constructional apraxia and map disorientation were present. No visual agnosia was found. The clinical picture remained grossly unchanged until the patient's death in August 1979. Necropsy showed, in addition to a right temporal herniation and a right calcarine infarction, tumour infiltration of the posterior two-thirds of the medial part of the parietal lobe and of the cuneus, extending from the cortex to the hippocampal formation.

*Case 3* (*B.T.*)

This 57-yr-old right-handed woman had a 3 wks history of progressive and febrile headache associated with numbness of the left hand Neurological examination showed left-sided hemiparesis, astereognosia, tactile and visual extinction, and dressing apraxia CT scan demonstrated a necrotic lesion of the right parietal lobe. At operation in April 1981, the posterior parietal cortex was incised and a purulent cavity lying underneath was evacuated. Diagnosis of pyogenic abscess was made. Her postoperative course was uneventful. Our first neurobehavioural examination took place in September 1981 Reduced finger skills of the left hand were the only motor deficit still present Position sense was mildly altered on the left side but tactile perception, graphaesthesia and stereognosis were unimpaired. Visual acuity was 10/10 bilaterally. Perimetry showed normal visual fields when tested with a large and bright spot, but a mild shrinkage of the left visual field on the smaller isopters Ocular movements were full. There was a mild constructional apraxia. No evidence of motor or hemispatial neglect was found. Topographical orientation was poor on a map but normal in real places The patient could recognize accurately objects, colours, faces and overlapping pictures. She was mentally alert and had no deficit for language, memory, perception of body image or praxis.

The patient was followed up over the next 3 yrs, during which partial recovery of the optic ataxia was observed.

*Case 4* (*P D.*)

This 55-yr-old right-handed diabetic man suffered a moderate left hemisphere stroke in May 1977 with a motor deficit of the right hand which resolved almost completely over the next few wks. Angiography showed atheromatous stenosis of the left internal carotid syphon. CT scan performed 3 months later showed a well-defined hypodensity in the left superior parietal lobe. On examination in August 1977, there was only slight weakness of thumb-index grip and moderate slowing of alternating finger movements on the right side. The right arm was relatively hypokinetic and neglected. Minimal sensory deficit, with astereognosia only for 2-dimensional geometrical forms, was noted in his right hand. Perimetry showed a full visual field with the stronger stimulus but a minor constriction of the right hemifield for the smaller isopters. Perception of the relative position of objects was preserved in both hemifields. There was no visual extinction on double field stimulation but single field presentation of 2 or more objects in the right field often led to extinction of the most peripheral one. Ocular movements were full and OKN was symmetrical. Examination for limb apraxia showed that gestures performed by the right hand were often slow and clumsy rather than apraxic. The left hand, sometimes preferentially used, executed correct gestures. There was a moderate constructional apraxia. Language and memory were fair. There was no disorder of body image, or hemispatial neglect or spatial disorientation. Visual recognition of objects, colours, faces and embedded figures was normal.

*Case 5* (*P.P.*)

This 72-yr-old right-handed man with a history of diabetes and transtibial amputation complicating severe leg arteriopathy, suffered a stroke 1½ yrs previously with consequent motor weakness and sensory impairment of his right arm. The initial deficit had resolved but the patient remained impaired by a 'loss of precision' of movements performed with his right hand. On examination in August 1978, he had no muscle weakness but he showed marked right limb hypokinesia. His right arm lay semiflexed, the hand being closed and pointing slightly forwards Movements of the right hand were slow. His reluctance to use that hand led him to use preferentially the left hand to eat There was mild impairment of position sense of the right fingers with a variable right sensory extinction Visual fields were normal on confrontation Distance and relative position of objects were well evaluated in each hemifield. Stereopsis was normal Ocular movements were full except for a slight saccadic difficulty for rightward adversion. The patient also showed a severe constructional apraxia and a moderately severe bilateral ideomotor and ideational apraxia, slightly more on the right side. Mental status was good and there was no language or memory deficit. Writing was slow but accurate. Body image, visual recognition of objects, colours and faces, were normal. Orientation on a map was fair.

*Case 6* (*J R.*)

This 53-yr-old right-handed man had a stroke in November 1978, which resulted initially in a right hemiplegia, worse in the lower limb, and an expressive aphasia. Cerebral angiography showed a left anterior cerebral artery occlusion. CT scan revealed a left hemisphere infarction involving the cingulate and anterior callosal region and the posterior parietal convexity. No embolic source was found. A few days later, the aphasia and hemiplegia had cleared. A transient callosal dysconnection syndrome was then suspected because of tactile anomia of the left hand and a left ear extinction in dichotic listening.

Our evaluation was prompted 6 wks postonset by the patient's complaints of 'missing' objects with his right hand. Although he had no motor deficit, even minimal, tapping finger movements were equally fast in both hands, he exhibited a striking hypokinesia of the right half of his body. Movements performed with the right arm or leg were slow and awkward. He initiated all manual activities with the left hand, the other arm being usually held in a flexed and adducted position. No sensory deficit was found. Visual acuity was 7/10 bilaterally. Visual fields were normal on perimetric examination, provided the right aphakic eye would be fitted with a +12 dioptres corrective lens. Objects and colour naming, estimation of distances and of line orientations, were not impaired in either visual hemifield There was no extinction with bilateral stimulation or when 2 or 3 objects were simultaneously presented in the right visual field. Ocular movements were full and OKN was symmetrical Memory and oral language were excellent Severe apraxia was present The patient had a bilateral ideomotor apraxia, slightly worse on the left arm, that resulted in a failure to perform gestures to verbal command or to imitation in approximately 50% of instances. Pantomime recognition was excellent. Bilateral ideational apraxia was also present, with a failure to use real objects in about 40% of instances. A constructional apraxia was also found. Gerstmann's syndrome was present in a complete form, associating severe agraphia with sparing of spelling abilities, acalculia for oral or written material, right-left confusion and a moderate finger agnosia. A moderate form of autotopagnosia was also present, as the patient could designate correctly only 8 of 16 body parts. There was no visual agnosia, or topographical disorientation Signs of right hemispatial neglect were also noted in writing and drawing. The patient only used the leftmost part of the paper. In reading, he sometimes missed small words on the right extremity of the lines No omission was found, however, in crossing out line segments.

Repeated evaluations were performed. Right hypokinesia, ideomotor apraxia and Gerstmann's syndrome had largely recovered over the next 2 yrs, but optic ataxia was still present 7 yrs later.

*Case 7 (A.V.)*

This 42-yr-old right-handed male developed a dense right hemiplegia and transient loss of consciousness shortly after a small nasal surgical procedure in March 1979. CT scan showed extensive infarction in the left superficial sylvian artery territory, worse in the posterior parietal region. It was thought that infarction was caused by emboli from a dissecting aneurysm of the left extracranial carotid artery revealed by angiography. The patient was treated conservatively. Over a 1 month period, his motor function had markedly improved and he showed only a mild expressive aphasia

He was referred to us 5 months postonset because of his persisting complaints of 'numbness' of his right arm. The patient was moderately depressed His attention, oral language and memory were good. Motor strength was only minimally altered with weakness of the thumb-index grip and slowed alternating finger movements. Moreover, the right arm tended to be neglected. Sensations in the right hand were slightly impaired, with decrease of position sense of fingers, minimal astereognosis, agraphaesthesia and tactile extinction. Visual acuity was 10/10 bilaterally Visual fields were normal on perimetry Perception of objects, colours and spatial localization was preserved in both visual fields. There was no evidence of hemispatial neglect. Ocular movements were normal. Severe bilateral ideomotor apraxia was present (failure to imitate or demonstrate use of common objects in 50% of instances) Moderate ideational apraxia could also be demonstrated (failure to pantomime and demonstrate use of real objects in 30% of instances) Pantomime recognition was fair Gerstmann's syndrome was present with severe agraphia and acalculia. There was no visual agnosia. Spatial orientation and constructions were good.

Six yrs postonset, the patient remained disabled by a marked slowness of his right arm, despite good recovery of the optic ataxia. Signs of agraphia and acalculia and right tactile extinction were still present.

*Case 8 (J C)*

This 56-yr-old right-handed hypertensive man had mental confusion and right sensory-motor deficit following headache of acute onset in October 1982. A circumscribed intracranial haematoma located in the left parieto-occipital region was diagnosed by CT scan. The clinical picture improved within a few days Our examination was carried out 4 wks postonset. The patient was alert and attentive. He had no oral language or memory disorder. Motor strength, skills and somatosensory sensations were normal on both sides but there was some evidence of a moderate hypokinesia of the right arm, especially while walking. Visual acuity was 6/10 for the right eye, 3/10 for the left one Visual fields were normal when tested with a bright spot on perimetry but a right visual field shrinkage was revealed by a dimmer spot. Subtle perceptual and attentional deficits were demonstrated clinically in the right visual field Thus the patient had no difficulty in naming single objects presented in either visual field but he would often fail to recognize the rightmost object when 2 of them were simultaneously presented in a right single field condition although this was infrequent in a double field condition. Colours could not be seen in the right hemifield, but were weakly perceived in the left field Perception of line orientation was good in both hemifields and there were only a few errors in estimating distance and relative position of objects in the right compared with the left field Some right hemispatial neglect was present in drawing and writing although there was no omission in crossing out line segments Ocular movements were normal and OKN symmetrical. A constructional apraxia was found A moderate Gerstmann's syndrome with a predominant agraphia was also noted. Ideomotor praxis and spatial orientation were well preserved.

Optic ataxia had partly recovered 3 months later

*Case 9 (G.B)*

This 75-yr-old right-handed physician had a left transient sensory-motor ischaemic attack in January 1984. He had a moderate stroke in March 1984 resulting in motor 'misuse' of the right side of his body CT scan disclosed two left hemisphere lesions, one in the medial, superior and posterior part of the parietal lobe, the other in the premotor area. Contrast infusion resulted in 'gyral' enhancement of the parietal lesion suggestive of a recent infarction. A diagnosis of border zone infarct was made on these data. Over the ensuing 2 months, the patient experienced 2 transient episodes of muscle weakness on the right side of his body. His condition then remained stable On examination in September 1984, muscle strength and skills were normal. However, he had a marked right-sided motor hypokinesia. The patient preferred to use his left hand, the right hand adopting curious postures at rest, being semiflexed in a prone position. Motor activity of the right hand was always slow and awkward. Pure astereognosis and reduced graphaesthesia were noted in the right hand. Visual acuity was 10/10 bilaterally Visual fields were completely normal on perimetry. Recognition of objects, colours and faces was unimpaired Estimation of distances, relative localization of objects and line orientation were normal in both hemifields. A moderate Gerstmann syndrome was present with slightly impaired finger denomination, acalculia, dysgraphia, and right-left confusion on the examiner. Constructions and topographical orientation were well preserved. There was no sign of hemispatial neglect Ocular movements were normal except for decreased OKN when the stimulus moved leftwards. Mental status was normal; language, memory, writing, body image and praxis were well preserved.

*Case 10* (*J.M.*)

This 56-yr-old right-handed man experienced in March 1984 several brief episodes of visual hallucinations in his right visual field consisting of vertical black bars moving horizontally The epileptic nature of these episodes was recognized 6 months later when the patient came to medical care because of a permanent 'disorder' in his right field of vision. He complained chiefly of a 'poor appreciation of distances' with his right hand on his right side of vision. For example, he had difficulty in writing down numbers in columns for calculation and in filling a glass of water when holding the bottle with his right hand He had no motor or skill deficit, or sensory impairment. Visual acuity was 10/10 bilaterally. Stereoacuity was moderately impaired on the TNO test. A right inferior homonymous quadrantanopia was shown by perimetry. In the remaining part of the right hemifield, there was no visual extinction and no defect for object and colour recognition Estimation of distance and relative position of objects, perception of line orientation and of motion were preserved in each hemifield. Ocular movements were full but OKN was slightly decreased when the stimulus moved leftwards. His mental status was excellent. There was no deficit of language, memory, praxis or body image Constructions and topographical orientation were good and there was no evidence of hemispatial neglect or limb akinesia. CT scan showed a 5 cm left occipital tumour, located mainly in the cuneus and surrounded by oedema. Surgical removal in September 1984 led to a diagnosis of malignant melanoma. His postoperative course was uneventful. In July 1986, optic ataxia persisted in a milder form, and in his everyday life the patient had still to fixate objects before reaching for them.

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# PHYSIOLOGICAL CONSEQUENCES OF ANTISERUM-MEDIATED EXPERIMENTAL DEMYELINATION IN CNS

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## SUMMARY

To study the pathophysiology of immunologically mediated demyelination in the central nervous system (CNS), we injected 20 to 30 $\mu$l of polyclonal antigalactocerebroside serum (AGC) into the lower thoracic dorsal column of the spinal cord in 20 Wistar rats. AGC-injected spinal cords contained areas of fascicular demyelination adjacent to the focus of axonal degeneration at the injection site. Somatosensory evoked potentials were recorded serially after tibial nerve stimulation. In 85% of AGC-injected animals, the following characteristics were observed by 3 days after injection: (1) decreased amplitude of the cortically generated potential (P15); (2) failure of transmission of high-frequency (50 Hz) impulses (rate-dependent block); (3) delayed conduction velocity of the compound action potentials through the lesion. None of these changes was seen in 90% of 20 rats injected with normal saline or control rabbit sera. In 7 rats with acrylamide-induced axonopathy or wallerian degeneration, the rate-dependent block was not observed. The onset of clinical symptoms (hindlimb ataxia) in AGC-injected rats was best correlated with development of the rate-dependent block. Clinical recovery was observed by 14 days after injection concurrent with restoration of P15 amplitude, when the rate-dependent block and decreased conduction velocities were unchanged. High-frequency-resistant conduction was re-established much later than clinical recovery in 3 rats. These findings suggest that failure of high-frequency impulse transmission may produce clinical symptoms and that a central adaptive mechanism to remodulated trains of impulses plays a role in clinical recovery from CNS demyelination.

## INTRODUCTION

In the traditional approach of clinical neurology, symptoms can be localized to discrete neuropathological lesions. This approach, however, has been challenged by the pathology of multiple sclerosis (MS), in which the size, number and distribution of demyelinative plaques is often greater than expected clinically (Waxman, 1981). Silent plaques without clinical manifestations are frequently encountered (Mackay and Hirano, 1967; Ghatak *et al.*, 1974). Similarly, subclinical lesions are detected by markedly prolonged evoked potential latencies (Halliday *et al.*, 1972; Chiappa, 1980). Remission of the clinical symptoms often occurs too early to be ascribed to remyelination, which is incomplete in MS (Davis, 1970;

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McDonald, 1974*a*, *b*; Prineas and Connell, 1979), and yet clinical recovery is complete in many cases. These clinicopathological discrepancies suggest that demyelinated fibres may transmit biologically useful information.

There have been several physiological studies on experimental models of demyelination in the central nervous system (CNS) (McDonald and Sears, 1970*a*, *b*; Mayer, 1971; Smith *et al.*, 1979, 1981; Foster *et al.*, 1980). McDonald and Sears (1970*a*, *b*) demonstrated decreased conduction velocities, prolonged refractory periods of transmission and impaired ability to transmit high frequency impulses (*see also* McDonald, 1974*b*) in single demyelinated CNS axons. Smith *et al.* (1979, 1981) showed restoration of high frequency-resistant conduction following CNS remyelination in serial antidromic recordings from the saphenous nerve in the cat. Bostock and Grafe (1985) demonstrated conduction failure after 10 to 50 Hz of tetanic stimuli in demyelinated rat spinal root axons. Although these studies made note of the clinical signs in animals with experimental demyelination, clinical and electrophysiological correlations could not be made in a serial manner because the electrophysiological analyses were based on acute experiments (McDonald and Sears, 1970*a*, *b*; Foster *et al.*, 1980; Bostock and Grafe, 1985) or were not accompanied by clinical signs (Smith *et al.*, 1979, 1981). The previous studies used a variety of methods to produce demyelination: mechanical (Mayer, 1971), toxic (diphtheria toxin; McDonald and Sears, 1970*a*, *b*; Bostock and Grafe, 1985) or chemical (lysophosphatidyl choline; Smith *et al.*, 1979, 1981; Foster *et al.*, 1980). They were accompanied by variable degrees of remyelination, little in the case of diphtheria toxin (Harrison *et al.*, 1972) and nearly complete in the case of lysophosphatidyl choline (Smith *et al.*, 1981; Blakemore *et al.*, 1977).

We believe that serial correlative studies of a model with immunologically mediated demyelination is more relevant to the understanding of the pathophysiological basis of symptoms in MS. The role of humoral factors in the development of demyelination in CNS has been emphasized (Lisak, 1980; Prineas and Graham, 1981; Wisniewski *et al.*, 1985). Antiserum to a major lipid component of myelin, galactocerebroside, has been shown to induce demyelination and remyelination in CNS (Sergott *et al.*, 1984, 1986). In this study, we have examined somatosensory evoked potentials (SEPs) and clinical signs *serially* in rats after injection of antigalactocerebroside (AGC) into the spinal cord. Although SEPs have certain shortcomings inherent to recording volume-conducted potentials (Kaji *et al.*, 1986) and reflect orthodromic conduction that may be contaminated by postsynaptic potentials, they offer advantages of monitoring conduction throughout the neuraxis, of being relatively noninvasive and of providing an opportunity to correlate the conduction changes with clinical signs during the evolution and resolution of a focal experimental CNS demyelinative lesion (Kaji and Sumner, 1986). The present study sheds light on the following specific problems. (1) What is the nature of conduction changes and their time course in immunologically mediated demyelination? (2) Are the conduction changes potentially reversible? (3) What is the physiological basis of development and recovery of clinical signs?

## MATERIALS AND METHODS

### *Preparation of antisera*

Antigalactocerebroside (AGC; titre of 1:128 or greater as measured by agglutination of liposome containing galactocerebroside; Fry *et al.*, 1976) was prepared by immunizing New Zealand rabbits (Saida *et al.*, 1979). Normal saline and control rabbit sera were used for control studies. The control sera included normal rabbit sera and sera from rabbits immunized with complete Freund's adjuvant (CFA) alone or CFA plus bovine serum albumin (BSA). AGC and control sera had been kept frozen (−70° C) until used, and fresh guinea pig serum (GPS) was supplemented (20% by volume) as a source of complement before injection. In some animals, 1:5 diluted AGC or control sera was injected. Heat-inactivated AGC (56° C, 30 min) with or without GPS was also prepared to determine whether the activity of AGC was complement-dependent or not.

### *Preparation of recipient animals*

Forty-seven male Wistar rats weighing 350–500 g were used. Six animals were injected with normal saline, 9 with control rabbit sera (5 from normal rabbits, 2 from a rabbit immunized with CFA and 2 from a rabbit immunized with CFA plus BSA), 15 with AGC, 5 with heat-inactivated AGC alone and 5 with heat-inactivated AGC plus GPS.

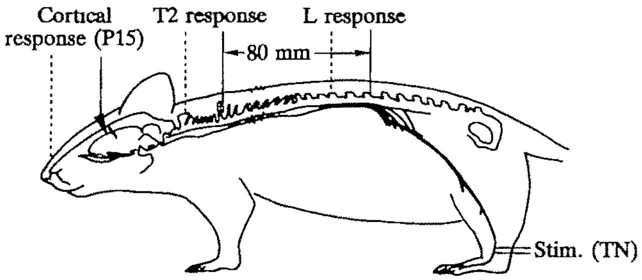

FIG. 1. An illustration of the electrode arrangement. Solid lines indicate the electrodes connected to grid 1 of the amplifier and broken lines are those connected to grid 2. Negativity at grid 1 was displayed upwards in the recordings. The stippled area is the site of laminectomy for injection. TN = tibial nerve CCV (central conduction velocity) = 80 mm/T2-L

Rats were anaesthetized by the intraperitoneal injection of a mixture of ketamine 100 mg/kg, xylazine 10 mg/kg and atropine 0.05 mg/kg, supplemented by inhalation anaesthesia with halothane(1–4%)-oxygen for recording spinal cord potentials. Halothane was not used for recording cortical SEPs, because it reduced the amplitudes of cortical potentials (Nash *et al.*, 1977). Ketamine produced no changes in the amplitude. The rats were fixed with a stereotaxic apparatus. The midline dorsal skin was incised aseptically over the thoracic vertebrae and laminectomy of the T6 vertebra was performed. The test serum (20–30 μl) was injected with a 30.5 gauge needle attached to a microsyringe. Because some reflux of the injected serum was observed under the operating microscope, the actual injected volume was estimated to be below 20–30 μl. Injection was made in the midline dorsal column of T8–9 cord segment at the depth where the bevel was buried (approximately 1 mm) with a microdrive. Injection was slowly made over 2 min and the precise injection site was chosen to avoid surface blood vessels. During injection the depth of anaesthesia was adjusted to minimize the movement of the spinal cord due to respiration, and in some animals 4% agar was placed on the spinal cord before injection. In several injections, coded sera were used.

For comparison, dorsal columns at the site of laminectomy were destroyed mechanically with the tip of the needle to produce wallerian degeneration in 4 rats. Two out of 4 rats had larger lesions that made them paraplegic after the operation, and the other 2 had smaller lesions that left them ambulatory. Bilateral lesions of the dorsolateral quadrant of the cord were made in 2 rats to examine the clinical signs caused by these lesions. Care was taken to avoid blood vessels in order not to cause compression by a haematoma. An additional 3 rats were injected with acrylamide (20 mg/kg/day) subcutaneously for 14 days to produce distal axonopathy.

### *Somatosensory evoked potentials*

For serial recordings from the primary somatosensory cortex, an aseptic surgical incision in the midline of the scalp overlying the coronal suture was made and small stainless steel screw electrodes (diameter 0.8 mm, length 2 mm) were fixed with a drill. Care was taken not to penetrate the dura. A positive potential from the primary somatosensory cortex (P15; figs 1, 3) was recorded at the midpoint between the insertion of the temporal muscles and the sagittal suture and 1 mm rostral to the coronal suture (Woolsey, 1958; Wiederholt and Iragui-Madoz, 1977). P15 was preceded by a negative potential in some animals (Kaji *et al.*, 1986). The cortical response was recorded from the side contralateral to the stimulation with a reference electrode attached to the nose. The screw electrodes were left on the skull throughout the period of observation and the scalp was opened and sutured every time the recording was made. Animals with displaced electrodes were excluded from analysis. Minimal tissue reactions to the screw electrodes were noted at the time of pathological study.

Rostral spinal cord potentials (T2 response; figs 1, 3) were recorded bipolarly with shielded needle electrodes (DISA) positioned on the laminae of the second thoracic (T2) and the second cervical (C2) vertebrae. Interelectrode distance was 2 cm. Negativity at the T2 electrode was displayed upwards. We used bipolar recordings to minimize muscle and cardiac artefacts, which would otherwise have greatly distorted the waveform in monopolar recordings. Bipolarly recorded action potentials are triphasic or tetraphasic, depending on the interelectrode distance and the intervening volume conductor (Buchthal and Rosenfalck, 1966; Kaji and Sumner, 1987). In either case, the initial positive-to-negative deflection represents the arrival of the depolarization wavefront at the electrode proximal to the stimulation site (T2). In so far as the interelectrode distance is kept constant, the duration of bipolarly recorded volume-conducted potentials reflects the duration and conduction velocity of the potentials directly recorded from the nerve (Buchthal and Rosenfalck, 1966). Therefore temporal dispersion due to decreased conduction velocity can be assessed with bipolar leads.

When the spinal cord underlying T2 was stimulated after cutting the ventral roots of the lumbar and upper sacral segments, the compound action potentials recorded antidromically from the tibial nerve at the ankle had the same onset latency as the orthodromic response (fig. 3). The fastest conducting potential was therefore a presynaptic volley.

Cauda equina potentials (L response; figs 1, 3) were obtained with bipolar electrodes placed 2 cm apart. The distance between the caudal electrodes of the T2 and L responses was 80 mm. The generator of the L response was confirmed to be the cauda equina because the lumbar electrodes were overlying the cauda equina at the pathological studies and the initial negative spike of the L response was intact immediately after isolating the cauda equina from the spinal cord.

Stimulating electrodes were at the ankle overlying the tibial nerve. Electric pulse stimuli of 0.1 ms duration were applied at a rate of 5 Hz for the cortical response (P15). For T2 and L responses, 10 Hz was chosen to avoid dorsal root reflexes (Casey and Oakley, 1972). We also used 50 Hz stimulation for spinal potential recordings to examine the effect of high-frequency stimulation. Intensities were adjusted to 10–20% above the motor threshold.

Potentials were amplified with a band pass of 20–2,000 Hz and averaged for 50 responses (P15), 250 responses (T2 response) or 20 responses (L response) with an analysis time of 50 ms (cortical response) or 20 ms (other responses) by a computer (TECA TD20). Because an automatic artefact rejection mode was used to suppress large cardiac artefacts in recording the T2 response, the total number of stimuli applied for each averaging ranged approximately from 300 to 400. There was no significant difference in the number of stimuli required to average 250 times among animals with normal or abnormal T2 responses in our preliminary series. Recordings were made separately from each recording site and automatically calibrated by the computer (TD 20). At least 2 traces were superimposed to assure the reproducibility. Throughout the experiments, rectal temperature of the rat was maintained between 36-37° C by a heating lamp.

### *Analysis of SEP data*

A conduction velocity in the spinal cord (central conduction velocity, CCV) was calculated by dividing the distance (80 mm) by the interval between the onsets of the T2 and L responses (fig. 1). The onset of the T2 response was measured to the peak of the earliest reproducible positive-going deflection followed by negative-going deflection or the onset of the earliest reproducible negative-going deflection.

The effect of body weight on CCV was examined in 40 normal control animals. CCV correlated with body weight in animals under 350 g (correlation coefficient = 0.65, n = 18), and it did not in animals weighing between 350-500 g (correlation coefficient = 0.31, n = 22). We therefore used animals weighing over 350 g in the other studies. The normal value for CCV in those over 350 g was $42.6 \pm 2.7$ m·s$^{-1}$ (n = 37). CCV was considered to be decreased if lower than 35.85 m·s$^{-1}$ (mean −2.5 SD).

In normal control rats, T2 responses after high frequency (50 Hz) stimulation did not change greatly from those after 10 Hz stimulation (figs 3B, 4A, before injection). The amplitude of T2 was measured from the bottom of the initial positivity to the peak of the following negative deflection. Amplitude ratios of T2 responses after 50 Hz stimulation to that after 10 Hz stimulation were $0.92 \pm 0.105$ (n = 28) in normal controls. Onset latency differences of T2 between 10 and 50 Hz stimulation were $0.04 \pm 0.048$ ms (n = 28). An amplitude ratio less than 0.66 (mean −2.5 SD) or a latency delay greater than 0.16 ms (mean +2.5 SD) was taken as evidence of failure of high-frequency impulse transmission or rate-dependent block (RDB; fig. 4). Amplitudes of P15 were measured from the baseline or, if present, from the preceding negative peak. Because the absolute value of the amplitude was variable from animal to animal, amplitude ratios of P15 to the preinjection value were measured. Variation of the amplitude ratios in the controls without injection were $90.42 \pm 28.5\%$ (n = 21), and a ratio smaller than 19.17% (mean −2.5 SD) was considered to be a significant amplitude decrease or P15 *block*. (We use the term 'block' here to indicate blockade or significant amplitude reduction of the response and it does not necessarily imply focal conduction block in myelinated axons.) The latency difference between the onset of the L response and P15 (L-P15) was measured as an index of conduction time from the cauda equina to the sensory cortex.

### *Clinical assessment*

Clinical signs of a dorsal column lesion were evaluated by putting the animal on a smooth surface to observe the hindlimb posture (placing reaction; Denny-Brown, 1966). Because the corticospinal tract in the rat is situated deep in the dorsal column (Brown, 1971), hindlimb weakness and spasticity were also checked. The diagnosis was based on agreement between 2 investigators (R.K. and A.S.).

Twelve rats were killed with an overdose of pentobarbital and perfused with 3% glutaraldehyde in 0.1 M phosphate buffer. The spinal cords including the injection site were removed, immersed in glutaraldehyde, postfixed in 2% osmium tetroxide, dehydrated in graded alcohols and propylene oxide and embedded in epoxy resin. Semithin sections were stained with methylene blue-Azur II and counterstained with basic fuchsin.

## RESULTS

### *The lesion*

Oedema was a prominent feature at the site of injection until 3 days after injection, and was equally observed in both AGC and control sera-injected groups. In the AGC-injected group, however, spinal cords obtained later than 3 days after injection contained areas of fascicular demyelination adjacent to a focus of axonal degeneration at the tip of the needle tract (fig. 2). The lesion usually involved the whole area of the dorsal columns except for the deepest portion and extended for 8 to 10 mm longitudinally. There was a tendency for the lesion to extend longitudinally along fibre tracts. The cross-sectional areas of the lesion ranged from approximately 2.0 to 2.5 mm$^2$ in the vicinity of the injection site,

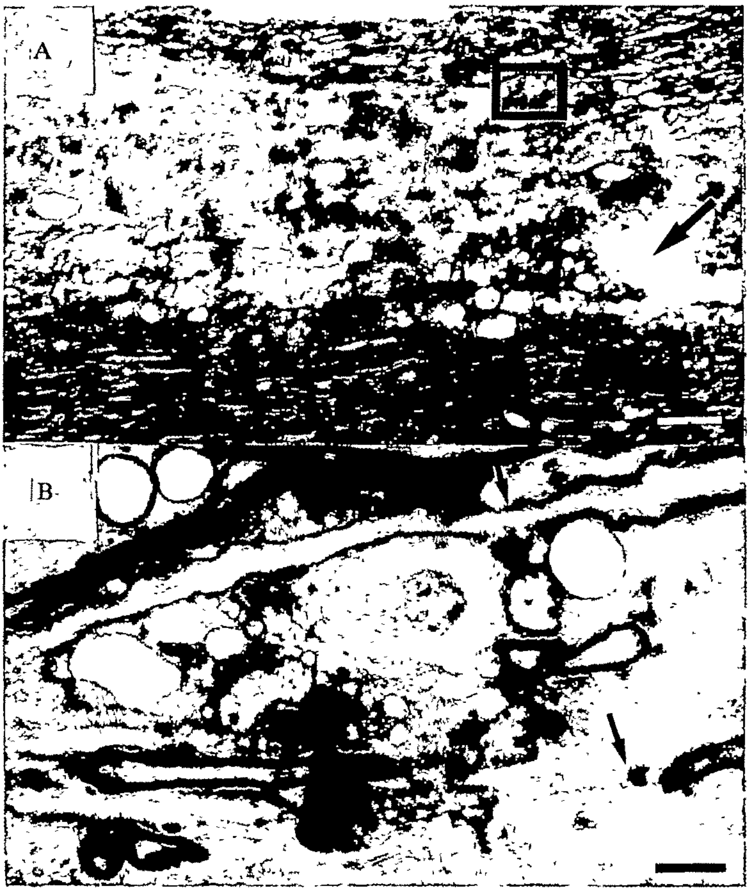

FIG. 2. A, area of fascicular demyelination in the T9 dorsal column adjacent to a focus of axonal degeneration at the tip of the needle tract (large arrow), 34 days after injection of AGC. Bar = 100 μm. Rectangle shows the area magnified in B. B, high power view of the transitional zone (rectangle in A) between intact and demyelinated areas. × 1 000. Rapid tapering of the myelin thickness was observed in 2 fibres (small arrows). At this stage thinly myelinated fibres were frequently observed (to left of upper arrow). Bar = 10 μm.

which was about a quarter to one-fifth of the whole cross-sectional area of the cord. The dorsolateral funiculus was involved unilaterally in a few rats, but the lesion never extended to the entire lateral column.

In animals over 30 days after AGC injection, very thinly myelinated fibres were consistently observed (fig. 2B). Those thinly myelinated axons were not found in rats earlier than 7 days after injection.

Two rats with milder symptoms out of the controls with mechanical injury to the cord showed a similar extent of lesions, which contained only wallerian degeneration. A detailed sequential and ultrastructural study will be the subject of a separate paper.

### *SEP findings*

*AGC-injected group.* This group of animals included 20 rats injected with AGC and 5 rats with heat-inactivated AGC supplemented by GPS as a source of complement. Similar conduction changes and time course were observed among these 25 animals. The latency of the T2 response was slightly delayed (0.08–0.32 ms) at 5 min after injection. Animals with a delay of more than 0.32 ms at this time point were excluded from analysis because of possible traumatic injection as described later. The earliest changes of conduction were observed in more than 40% of the animals within 3–6 h after the injection (figs 3A, 5, Table); rate-dependent blocks (RDB) of the T2 response, slight delay of CCV and changes of the waveform of P15 with normal amplitudes. Significant decrease of P15 amplitudes were usually observed after 6 h. These changes reached a maximum by 3 days after injection, at which time 20 out of 25 rats (80%) showed all of these findings. P15 amplitude decrease was not significant in 2 animals and no change was observed in 1 animal.

The most outstanding finding in this group was RDB, which was a significant reduction of the amplitude or delay of the latency of the compound action potentials conducting through the lesion (T2 response) after high-frequency stimulation (figs 3A, 4). L responses were always resistant to 50 Hz stimulation. When the T2 response was visible on the monitor during averaging, the first several responses could have normal latencies, but the latencies of the following responses gradually prolonged until a state of equilibrium was reached. In these instances, the latency of the first normal responses tended to be averaged out, resulting in a prolonged latency of the final waveform. In other instances, responses met the amplitude criterion for RDB.

RDB was not observed in animals with wallerian degeneration nor those with distal axonopathy due to acrylamide intoxication (fig. 4A, right). In 2 animals with RDB at 3 days after injection, the spinal cord was stimulated at the level of the T2 vertebra, and the antidromically conducted volley was recorded from the tibial nerve at the ankle (fig. 4B, right). The lumbar and upper sacral ventral roots had been cut to block orthodromic motor conduction. We observed RDB similar to that in the orthodromic T2 response. RDB was therefore not caused

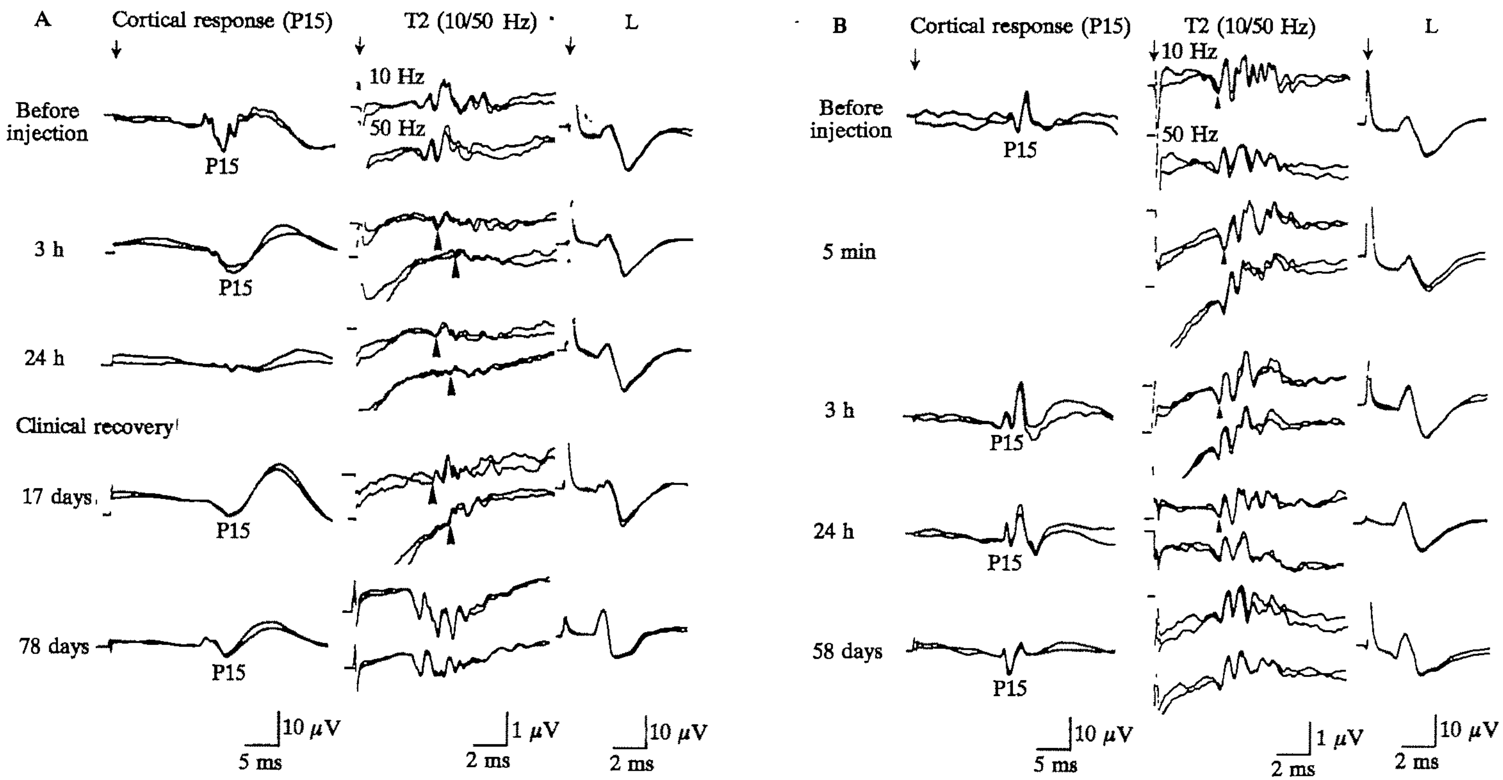

FIG. 3. A, a representative time course of conduction changes in an AGC-injected rat (Rat 150). The *lower* traces of the T2 response at each trial are after 50 Hz stimulation. RDB of the T2 response was observed as early as 3 h after injection (large arrow heads), and persisted after the rat had recovered clinically (17 days) Baseline shifts following the stimulus artefact in traces of T2 responses at 3 h, 24 h and 17 days were interferences due to cardiac artefacts phase-locked to the stimulus cycle by the artefact rejection mode. P15 regained a normal amplitude concurrent with clinical recovery. A high-frequency-resistant T2 response and the original waveform of P15 were restored at 78 days. B, a representative time course of conduction in a normal rabbit serum-injected rat (Rat 167). The *lower* traces of T2 at each trial are after 50 Hz stimulation. Baseline shifts were due to cardiac artefacts. No significant changes were observed except for a slight latency delay of the T2 response at 5 min after injection (small arrowheads). P15 at 5 min was not obtained because the effect of halothane on P15 amplitudes persisted at this time point.

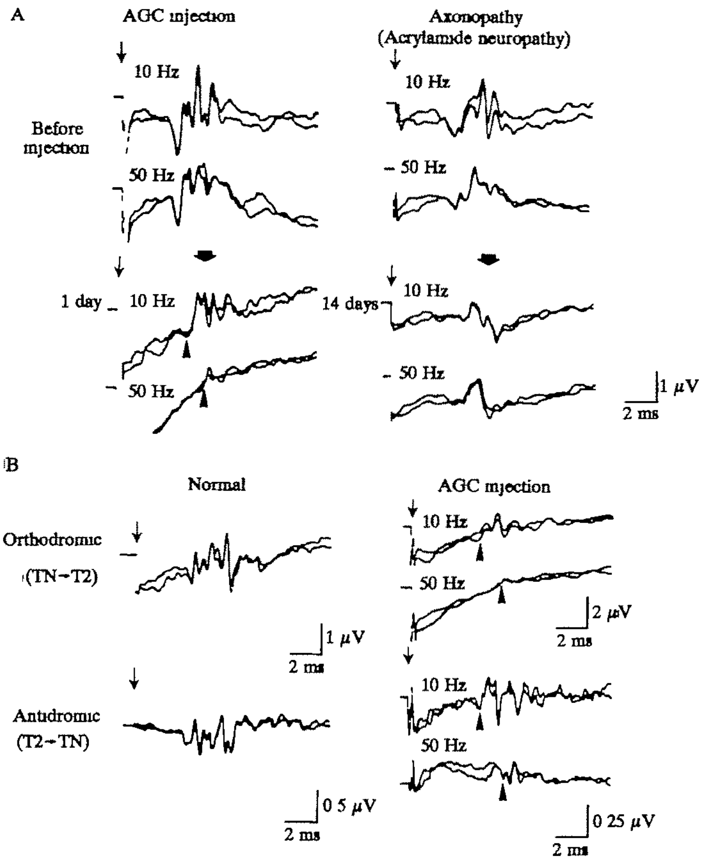

FIG. 4 *Rat 207*. A, comparison of conduction changes in rats before and after AGC injection (*left*) and acrylamide intoxication (*right*). In axonopathy due to acrylamide, RDB was not observed and the duration of the T2 response was shorter than that in the preinjection study. B, comparison of orthodromic T2 responses and antidromic responses after T2 stimulation in a normal rat and a rat 3 days after injection of AGC (*Rat 193*). Lumbosacral ventral roots had been cut to avoid orthodromic motor conduction. The antidromic response had the same onset as the orthodromic, and RDB was similarly observed in the antidromic response. TN = tibial nerve.

by postsynaptic potentials with long refractory periods but was a property of the presynaptic fibres.

The peak latency of P15 measured from the L response (L-P15) was delayed by 1 to 5 ms up until 14 days after injection compared with the preinjection value in some animals (fig. 3A; Table). In the other animals, cortical potentials had multiple peaks, and it was impossible to identify the P15 peak accurately. No significant temporal dispersion of the T2 response was observed, even when cortical potentials had dispersed multiple peaks (fig. 3A, 24 h). The peak of P15 was consistently identified later than 14 days after injection, although 1 animal showed a significantly reduced amplitude of P15 even after 60 days (Table). L-P15 interpeak latencies at this stage were 15.40 ± 1.18 ms (mean ± SD, n = 22), which was not statistically

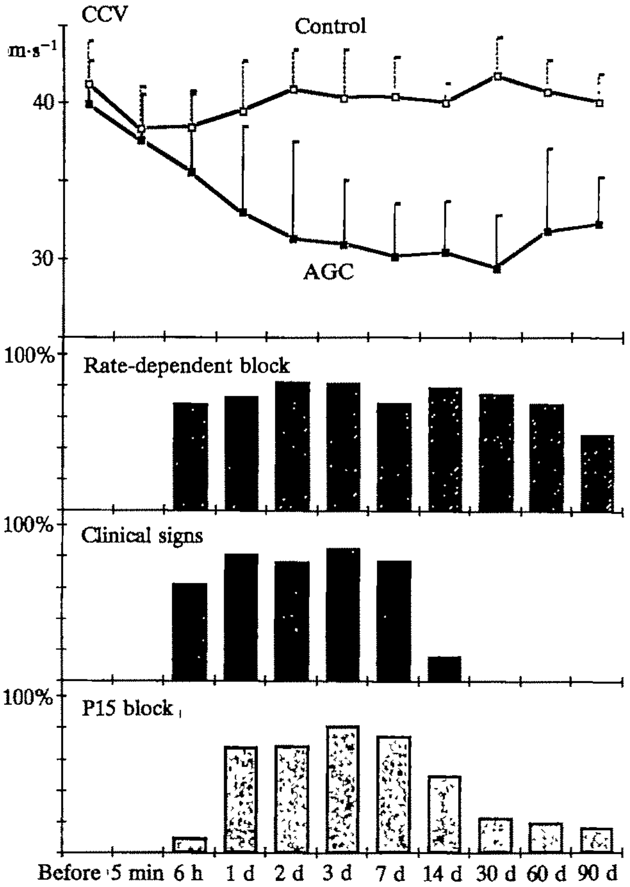

FIG. 5. Physiological and clinical changes in animals injected with AGC (or heat-inactivated AGC+GPS). Central conduction velocities (CCV), rate-dependent blocks (RDB) of T2 response, clinical signs and P15 blocks are shown. CCV changes in the control group (Control), injected with control sera, heat-inactivated AGC without GPS or normal saline, are also shown for comparison. No animals injected with AGC showed RDB at 5 min after injection. Clinical signs and P15 blocks were not examined at 5 min because the animals were still under anaesthesia. In Clinical signs, stippled area = hindlimb ataxia; filled area = paraplegia.

different from the preinjection value (14.77±0.87 ms; $P > 0.05$; Table). Recovery of P15 amplitude was observed as early as 14 days after injection (figs 3A, 5). In the long-term follow-up of these conduction changes, 3 out of 6 animals reestablished high-frequency-resistant conduction with normal CCV after 60 days (fig. 3A; Table). The waveform of P15 was also restored in these animals. In the total, CCV began to recover after 30 days until it reached a near-normal level by 90 days after injection (fig. 5).

*Control group.* This group comprised 6 rats injected with normal saline, 9 with control sera and 4 with heat-inactivated AGC. Slight latency shifts of T2 less than 0.32 ms were observed at 5 min after injection, which returned to preinjection

TABLE PHYSIOLOGICAL AND CLINICAL CHANGES AFTER AGC INJECTION*

| | *Before injection* | *5 min* | *−6 h* | *−1 day* | *−2 days* | *−3 days* | *−7 days* | *−14 days* | *−30 days* | *−60 days* | *−90 days* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| CCV | | | | | | | | | | | |
| AGC group | | | | | | | | | | | |
| Mean ($m \cdot s^{-1}$) | 39.92 | 37.65 | 35.54 | 32.99 | 31.33 | 30.97 | 30.14 | 30.44 | 29.45 | 31.79 | 32.32 |
| SD ($m \cdot s^{-1}$) | 2.77 | 2.92 | 5.19 | 5.55 | 6.21 | 4.14 | 3.42 | 3.32 | 3.43 | 5.38 | 3 03 |
| n | 41 | 37 | 16 | 33 | 24 | 17 | 8 | 12 | 16 | 8 | 6 |
| Control Group** | | | | | | | | | | | |
| Mean ($m \cdot s^{-1}$) | 41.23 | 38.34 | 38.46 | 39.5 | 40.86 | 40.34 | 40.39 | 40 05 | 41.75 | 40.73 | 40.08 |
| SD ($m \cdot s^{-1}$) | 2.75 | 2.75 | 2.12 | 3.2 | 2.58 | 3.08 | 2.56 | 1.21 | 2.247 | 2.1 | 1.83 |
| n | 37 | 37 | 9 | 25 | 14 | 14 | 14 | 8 | 2 | 8 | 6 |
| RDB | | | | | | | | | | | |
| Positive | 0 | 0 | 11 | 25 | 20 | 19 | 7 | 12 | 16 | 7 | 3 |
| n | 42 | 38 | 16 | 34 | 24 | 23 | 10 | 15 | 21 | 10 | 6 |
| Clinical signs | | | | | | | | | | | |
| Hind-limb ataxia | | | 10 | 18 | 16 | 10 | 6 | 1 | 0 | 0 | 0 |
| Spastic paraparesis | | | 0 | 0 | 1 | 2 | 1 | 1 | 0 | 0 | 0 |
| n | | | 16 | 22 | 22 | 14 | 9 | 12 | 16 | 8 | 6 |
| P15 block | | | | | | | | | | | |
| Positive | | | 1 | 15 | 9 | 9 | 3 | 4 | 3 | 1 | 1 |
| n | | | 10 | 22 | 13 | 11 | 4 | 8 | 13 | 5 | 6 |
| L-P15 | | | | | | | | | | | *15–90 days* |
| Mean ($m \cdot s^{-1}$) | 14.77 | | | | | | | | | | 15.40 |
| SD ($m \cdot s^{-1}$) | 0.87 | | | | | | | | | | 1.18 |
| n | 24 | | | | | | | | | | 22 |

* Includes animals injected with AGC or heat-activated AGC+GPS. ** Values of control sera or normal saline-injected group are shown for comparison.

values 1 day after injection (figs 3B, 5). In our preliminary study, animals that showed immediate postinjection latency increases of more than 0.32 ms failed to return to the preinjection value, indicating a traumatic injection. These animals were excluded from further analysis. No significant changes of CCV, amplitude ratios of T2 after 50 to 10 Hz stimulation or P15 amplitudes were observed thereafter (fig. 3B). These SEP findings were similar throughout this group with the exception of 2 animals (fig. 6). One rat (Rat 205) injected with normal rabbit serum showed a decreased amplitude of P15 without RDB or CCV delay. The other animal injected with heat-inactivated AGC (Rat 225) showed delayed CCV without RDB or P15 block.

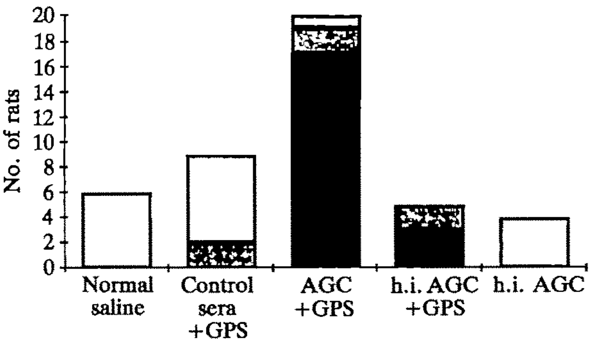

FIG. 6. Incidence of conduction changes in various groups. Filled area indicates the number of animals with all of RDB, CCV delay and P15 block. Stippled area is the number of rats with one or two of the above changes. Open area is the number of rats with no changes. h.i. = heat-inactivated.

*Wallerian degeneration and acrylamide intoxication groups.* In 2 animals with larger lesions out of 4 with wallerian degeneration, the T2 and P15 responses were totally abolished immediately after operation. There was no sign of recovery in the following 7 to 10 days, and both animals died by 14 days. In the other 2 animals with relatively smaller lesions, CCV was reduced (34.5 and 30.3 $m{\cdot}s^{-1}$) and the P15 amplitude was significantly decreased immediately after operation. RDB, however, was not observed. These findings remained unchanged over the following 90 days. Animals intoxicated with acrylamide showed decreased CCV within 14 days. T2 responses were shorter in duration than those in the preinjection study (fig. 4A, right).

### *Clinical correlation*

In more than half of the animals injected with AGC or heat-inactivated AGC + GPS, the first clinical sign appeared 3–6 h after injection (fig. 5); the animal could not land on a smooth surface without splaying the hindlimbs widely when lightly dropped, forelimbs first, onto a surface (hindlimb ataxia). Splaying of the hindlimbs was always bilateral. This sign was evident immediately after landing, after which the animal soon began to walk normally, suggesting that it was not due to weakness but to a defective placing reaction secondary to impaired proprioception (Denny-Brown, 1966). Responses to pin prick or other superficial stimuli were normal. By 3 days after injection, hindlimb ataxia was evident in more than 80% of the animals, and the development of hindlimb ataxia correlated best with the onset of RDB (fig. 5). Unexpectedly, most animals with hindlimb ataxia recovered clinically between 7 and 14 days after injection while the volley through the lesion still had RDB of the T2 response and decreased CCV. This clinical recovery coincided with the return of P15 amplitude (fig. 5). Three animals with hindlimb ataxia subsequently developed paraplegia and died of complications within 30 days. In the control sera-injected group, no clinical abnormalities were noted. In the animals with wallerian degeneration, the 2 with larger lesions showed paraplegia and the other 2 with smaller lesions had spastic paraparesis immediately after the operation. The former 2 did not recover and eventually died within 30 days of the operation. The latter 2 recovered much later than the recovery of the AGC-injected group (between 30 and 60 days after operation) with some residual spasticity. The rats with bilateral lesions in the dorsolateral quadrant of the cord showed paraparesis rather than ataxia.

## DISCUSSION

The present study disclosed a characteristic triad of changes in conduction after AGC injection: (1) decreased amplitudes of the cortically generated potential (P15 block); (2) failure to transmit high-frequency impulses through the lesion as indicated by RDB of the T2 response; and (3) slowing of the maximal conduction velocity of the compound action potentials through the lesion (decreased CCV). These changes began 3-6 h after injection and reached a maximum by 3 days after injection. Gradual recovery of the conduction velocity was observed, and in a few animals high-frequency-resistant conduction was reestablished by 90 days after injection.

Although the lesions showed prominent oedema until 3 days after injection and axonal degeneration adjacent to the injection site, there are several lines of evidence to suggest that these conduction changes were caused by demyelination. No animal showed all these changes in the groups injected with normal saline or control sera, in which a similar extent of oedema was observed. Oedema had resolved by 3 days after injection, whereas the conduction changes reached a maximum at this stage. No rate-dependent changes were noted in the animals that underwent wallerian degeneration or those with distal axonopathy due to acrylamide intoxication. The changes were at least partially reversible in contrast to the findings in wallerian degeneration. We therefore consider that the above changes are the specific consequences of CNS demyelination. Because there still remains a possibility that combined demyelination and axonal degeneration produced the conduction abnormalities, we use the term 'CNS demyelination' to include a demyelinative lesion with a minor degree of axonal degeneration, which is the usual pathological finding in human MS (McDonald, 1986).

The serum activity responsible for the triad of conduction changes appears to be complement-dependent, because preheating serum at 56° C for 30 min abolished the activity, and addition of complement restored it. As complement-added control sera including anti-BSA serum did not produce the triad, the activity seems to be mediated by antibodies to galactocerebroside like the CNS demyelinating activity of AGC evidenced morphologically (Sergott *et al.*, 1984).

Conduction block, conduction slowing and the inability to transmit high frequency impulses or prolonged refractory period of transmission were reported in demyelination induced by diphtheria toxin (Rasminsky and Sears, 1972; McDonald and Sears, 1970*a*, *b*; McDonald, 1974*b*; Bostock and Grafe, 1985) and lysophosphatidyl choline-induced demyelination (Smith *et al.*, 1979, 1981). It was not possible to observe conduction block directly in our model. The loss of the amplitude of P15 (P15 block) reflects a decrease in the number of volleys or extensive desynchronization of the volleys reaching the cortex (Kaji *et al.*, 1986). Because there was no significant temporal dispersion of the T2 response after AGC injection, we consider P15 block to be evidence of conduction block of the volleys through the lesion. Since most animals had recovered from P15 block by 30 days after injection in contrast to the persistent loss of P15 in acrylamide-induced axonal degeneration (Kaji and Sumner, 1986), we suspect that P15 block is due to demyelinative conduction block.

McDonald and Sears (1970*b*) proved delayed conduction velocity in a single demyelinated CNS fibre. Although our study could not determine whether the conduction delay is due to slowing in individual fibres or selective blockade of the fastest conducting fibres, at least the former is contributing to the delay, because the duration of the T2 response was not shortened as in acrylamide neuropathy in which selective loss of the fastest conducting fibres has been shown (Sumner and Asbury, 1975; Sumner, 1980).

Smith *et al.* (1979, 1981) showed that central remyelination could restore normal latencies and refractory periods of transmission. Although thinly myelinated fibres were found only in rats examined later than 30 days after injection, the present study does not provide conclusive morphological evidence for remyelination (Harrison *et al.*, 1972; McDonald, 1974*a*). Physiologically, however, recovery of high-frequency-resistant conduction was observed within 90 days after injection of AGC. Our model of CNS demyelination therefore seems to be a monophasic and physiologically reversible process.

The rate-dependent block (RDB) distinguishes AGC-injected animals from those with axonal degeneration. Because we averaged responses which could vary in latency during acquisition, the criteria for RDB may not be sensitive enough to detect slight latency changes due to high-frequency stimulation. In spite of this shortcoming, the frequency at which RDB was observed in our study (50 Hz) was lower than that in a single fibre study in diphtheria toxin-induced CNS demyelination (70 Hz; McDonald and Sears, 1970*b*; McDonald, 1974*b*) and was in close agreement with the stimulus frequency required to block conduction (10–50 Hz) in demyelinated ventral root axons reported by Bostock and Grafe (1985).

A frequency of 50 Hz corresponds to an interstimulus interval of 20 ms, which is considerably greater than the maximum refractory period of transmission (4 ms) in lysophosphatidyl choline-induced CNS demyelination (Smith *et al.*, 1979, 1981). Although failure to transmit high-frequency impulses in tetanic stimulation is closely related to prolonged refractory periods of transmission revealed by paired stimulation, the two are not the same phenomenon. The effect of tetanic stimulation is progressive during stimulation until it reaches a state of equilibrium. This progressive effect was once ascribed to intracellular accumulation of sodium ions (Rasminsky and Sears, 1972), which reduces the current available to excite the demyelinated segment, but more recently Bostock and Grafe (1985) have shown that conduction is blocked by a different mechanism. The demyelinated segment develops an increased threshold due to hyperpolarization brought about by the electrogenic sodium/potassium pump. Conduction failure in tetanic stimulation may have more important clinical implications than the prolonged refractory period associated with paired stimulation, because natural impulses are transmitted in bursts rather than in pairs.

In contrast to the markedly prolonged latencies of cortical SEPs in human MS, which often persist long after clinical recovery, we observed only minor and transient delays of P15. Several factors may account for this discrepancy. The extent of the experimental lesion was limited in this study, while patients with MS usually have more extensive or multiple lesions. The normal range of L-P15 interpeak latencies was so wide in our model that L-P15 fell into the normal range even in animals with prolonged CCVs. Consequently, the present model may not be sensitive enough to detect P15 delays in a small animal. Delay of the cortical response may reverse more rapidly in the rat because remyelination is likely to be more prompt and complete in the rat than in man (Blakemore, 1976; Prineas and Connell, 1979). Alternatively, continuous conduction through demyelinated fibres, which markedly prolongs conduction, might be established in human MS. If the present model of central demyelination is to be compared with human MS, it should be regarded as a model of the very early phase in the natural course of MS with a focal lesion.

The clinically observed hindlimb ataxia might conceivably be caused by lesions in the dorsal spinocerebellar tract or the spinocervical tract, as well as dorsal column lesions. In fact, the lesion extended unilaterally into the dorsolateral quadrant in a few animals. In the rat, however, the dorsal spinocerebellar tract is located diffusely in the entire lateral column (Zemlan *et al.*, 1978), and the spinocervical tract is overlapped by the rubrospinal tract (Giesler *et al.*, 1979; Brown, 1974). It is therefore highly unlikely that these sensory tracts could be involved without affecting other descending tracts. Bilateral section of the dorsolateral quadrants caused paraparesis rather than ataxia in this study. Moreover, it is unlikely that bilaterally observed hindlimb ataxia was caused by a unilateral lesion of dorsolateral funiculus. Transient volume effects or oedema due to the injection may also affect conduction in the dorsal spinocerebellar or spinocervical tract. However, hindlimb ataxia was not observed in rats injected with control serum of the same volume, and the ataxia persisted for more than 3 days after injection in AGC-injected rats, at which time morphological changes of oedema had resolved. In addition, transient latency delays ascribed to the volume effect of injection in control serum-injected rats had recovered by 24 h after injection (figs 3B, 5). Because some of the injected serum showed reflux into the subarachnoid space, there remains a possibility that the cauda equina or the root fibres were also involved. However, the cauda equina potentials (L response) showed no comparable change and this possibility is, at least physiologically, insignificant. It is therefore likely that hindlimb ataxia was mainly caused by the dorsal column lesion, and the clinical signs could be correlated with abnormal transmission of repetitive trains in the dorsal column axons recorded as the T2 response.

The onset of hindlimb ataxia coincided with the development of rate-dependent block and slightly delayed CCV (fig. 5). In some animals, the amplitude of the T2 response after 10 Hz stimulation was also reduced when compared with that before injection at this stage (fig. 3A). However, the T2 response at 10 Hz was not greatly reduced in amplitude in other rats presenting with hindlimb ataxia (fig. 4A, left). The first clinical deficit was usually observed when the P15 amplitude was still within normal limits, in contrast to nearly complete loss of P15 at the onset of clinical signs in acrylamide neuropathy (Kaji and Sumner, 1986) or the complete conduction block observed at the onset of weakness in the peripheral nerve demyelination (Saida *et al.*, 1980; Sumner *et al.*, 1982). The preservation of P15 amplitude in our model suggests that the primary afferent input was not greatly reduced or that any reduction was well compensated for by central amplification (Eisen *et al.*, 1982). Although it is likely that a reduced amount of primary afferent volleys plays a role in some rats, abnormal frequency characteristics of the primary afferent input seems to be essential in presenting clinical symptoms in rats without major reduction in the T2 amplitude. There was no marked temporal dispersion of the T2 response, which could desynchronize the impulses. Slight delay of CCV per se seems to have little clinical significance, because such a minor delay could occur naturally, secondary to lowered body or limb temperature, with no clinical deficits. Although reduced primary afferent volleys probably contribute to the symptoms, the RDB appears to play the most important role in the development of symptoms.

In the peripheral motor fibres, the frequency range of impulses encountered naturally is usually below 50 Hz (Norris and Gasteiger, 1955), and the function of the effector organ (muscle power) is mainly determined by the magnitude of the frequency and number of recruited motor units (Adrian and Bronk, 1929), not by the exact timing of impulses. In CNS, the highest frequencies occurring naturally are up to 100 Hz in the pyramidal tract fibres (Evarts, 1965) and up to 150 Hz in the thalamus (Mountcastle *et al.*, 1963) or 250 Hz in the muscle spindle afferents (Kennedy *et al.*, 1980). In addition, the information transmitted in the CNS is exquisitely coded in a frequency-modulated manner (Bindman and Lippold, 1981). The failure to transmit impulses of 50 Hz or more with the exact timing would therefore imply severely impaired neural coding. If we assume a similar mechanism of development of clinical symptoms in patients with MS, a slight compromise of the maximum frequency that nerve fibres can follow could result in severe clinical symptoms, because such a change might render the information uninterpretable by the postsynaptic neurons.

The present study also provides an important clue to clarify the mechanism of clinical recovery from a central demyelinative lesion. While the animal was recovering from hindlimb ataxia, no marked changes of the T2 potential through the lesion was observed, while the P15 potential from the sensory cortex was restored to a normal amplitude (fig. 5). If the recovery was due to the dispersion of oedema in the acute phase (McDonald, 1974*a*; Jacobson *et al.*, 1979), the T2 response should exhibit a comparable change. It might be possible to ascribe the recovery to the plasticity of the CNS that is usually seen in animals following dorsal column destruction (Denny-Brown, 1966). In fact, animals that underwent destruction of the dorsal column in this study also showed clinical recovery even without recovery of conduction, but in this case it took more than 30 days and some spasticity persisted. On the other hand, the animals injected with AGC showed much earlier and more complete recovery in spite of the similar extent of lesions, suggesting a different recovery process. It seems likely therefore that an adaptive process may take place at rostral nuclei to interpret impulses 'remodulated' by the loss of high-frequency components. It is possible that this remodulation occurs as a consequence of terminal arborization of the axons (Waxman, 1972), or synaptic reorganization (Tsukahara and Fujito, 1976; Brown and Ironton, 1977; Lee *et al.*, 1977), which can occur within 7-14 days.

In clinicopathological studies of MS, specific clinical deficits have been ascribed only to the demyelinated lesions, and little attention has been paid to the postsynaptic neurons that receive input from the demyelinated fibres. If we consider the clinical symptomatology in the light of interaction between the lesion and adaptive changes that may occur at synaptic relays, some of the clinicopathological discrepancies in MS might be resolvable.

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# A COMPARATIVE STUDY OF VISUOSPATIAL MEMORY AND LEARNING IN ALZHEIMER-TYPE DEMENTIA AND PARKINSON'S DISEASE

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## SUMMARY

Groups of patients with dementia of Alzheimer type (DAT) and idiopathic Parkinson's disease, together with age and IQ-matched normal controls, were compared on several computerized tests of visuospatial memory and learning. Two different groups of parkinsonian patients were studied: (1) a newly diagnosed group, early in the course of the disease, not receiving medication (NMED PD) and (2) a group later in the course of the disease, receiving medication (MED PD). The DAT and MED PD group were significantly impaired in both spatial and visual pattern recognition memory. The DAT group exhibited a delay-dependent deficit (over 0–16 s) in a delayed matching-to-sample procedure, but were not impaired at simultaneous-matching-to-sample. By contrast, the MED PD group showed delay-independent deficits in the delayed matching-to-sample test and both the MED PD and the NMED PD group were also significantly impaired in simultaneous matching. In a form of delayed response test, the subjects were required first to memorize and then to learn the locations of several abstract visual stimuli which varied progressively in number from 1 to 8. The DAT group were severely impaired in this conditional associative learning task. A significant proportion of patients, but none of the controls, in the NMED and MED PD group also failed the test at the levels of 6 or 8 items. There was a significant correlation between the performance on the first trial, memory score in the delayed response task and indices of clinical disability and disease duration in the patients with Parkinson's disease. The results are discussed in terms of the utility of the comparison between DAT and PD in characterizing the nature of the cognitive deficits in these conditions and their relation to those findings from animal neuropsychology which use comparable paradigms.

## INTRODUCTION

Progress in defining the neurochemical and neuropathological postmortem correlates of Parkinson's disease and dementia of Alzheimer type (DAT) has given

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impetus to the neuropsychological analysis of the cognitive deficits of these disorders. There is considerable evidence of a high incidence of dementia in patients with Parkinson's disease (Boller, 1983; Brown and Marsden, 1984; Quinn *et al.*, 1986) and of a considerable overlap between the neuropathological signs exhibited in Parkinson's disease and DAT (*see* Edwardson *et al.*, 1985 for a review), which now warrants a detailed comparison of the cognitive profiles of the two populations.

Previous evidence has shown that cognitive function can be impaired even early in the course of PD, prior to medication (Lees and Smith, 1983; Weingartner *et al.*, 1984) and the deficits often resemble those seen after frontal lobe damage both in medicated and unmedicated patients (Lees and Smith, 1983; Taylor *et al.*, 1986; Gotham *et al.*, 1988). By contrast, the first and most prominent symptom to occur in DAT is usually deterioration in memory and new learning (Corkin, 1982; Corkin *et al.*, 1984; McKhann *et al.*, 1984; Morris and Kopelman, 1986). There are substantial impairments in both verbal and nonverbal forms of recognition memory and free recall (Corkin, 1982; Corkin *et al.*, 1984) that are consistent with temporal lobe dysfunction.

Considering previous work on mnemonic function in Parkinson's disease, there have been somewhat conflicting reports. Several clinical studies have shown that patients with PD have deficits in memory and learning, particularly for visuospatial material (Reitan and Boll, 1971; Garron *et al.*, 1972; Loranger *et al.*, 1972; Mortimer *et al.*, 1982; Pirozzolo *et al.*, 1982; Boller, 1983) or if free recall is required (Weingartner *et al.*, 1984). However, a recent study of visual recognition memory in a large group of medicated and unmedicated parkinsonian subjects revealed no difference from a matched control group (Flowers *et al.*, 1984).

Until recently, the cognitive function of patients with DAT or PD has rarely been compared systematically within the same study (Sagar, 1984; Sagar *et al.*, 1985; El-Awar *et al.*, 1987). The study of visual memory and learning for nonverbal material is clearly important for this comparison, but also has some additional advantages. While linguistic function is largely intact in PD, it is often affected in DAT (Appell *et al.*, 1982) and such impairments may confound, as well as augment, mnemonic dysfunction. The use of visual, nonverbal material also enables comparisons to be made with the extensive nonhuman literature which is beginning to define the necessary neural and neurochemical substrates of visual memory and learning. This is particularly important in assessing the possible causal significance of postmortem neurochemical changes in dopaminergic, noradrenergic and cholinergic cortical systems (Edwardson *et al.*, 1985) to the cognitive dysfunction in PD and DAT. Studies of subhuman primates have begun to investigate the effects of specific lesions of these projections on aspects of visual memory (Brozoski *et al.*, 1979; Ridley *et al.*, 1986; Aigner *et al.*, 1987), but their relevance to DAT and PD depends on demonstrating the existence of analogous deficits in the human patients.

In the present study, computerized tests of different aspects of visual memory, using a touch-sensitive screen, were designed for comparing three groups and their age and IQ-matched controls. Patients with idiopathic Parkinson's disease were either newly diagnosed and not yet receiving medication (NMED PD), or later in the course and receiving medication (MED PD). The third group of patients was early in the course of DAT (DAT).

Complementary tests of visual pattern recognition and visuospatial recognition were included because of the possibility that, although DAT patients exhibit global deficits in recognition (e.g., Corkin, 1982), PD patients may show impairments restricted to spatial memory (e.g., Taylor *et al.*, 1986). The pattern recognition test is analogous to the type of serial recognition test used by Gaffan (1974) and Mishkin (1982) for testing visual memory for lists of objects in nonhuman primates. To strengthen this parallel, a matching-to-sample (MTS) procedure, with both simultaneous and delay components was also used in the present study. Mishkin (1982) has shown in monkeys that delayed nonmatching-to-sample (DNMTS) and serial recognition of objects are particularly sensitive to lesions of the temporal lobe. In order to make the MTS task sufficiently difficult for our human subjects, the complexity of the sample stimuli was increased by varying them along two dimensions, colour and shape.

The separate tests of visual pattern and visuospatial memory are related to the final test, which requires both forms of memory. In this test, the subject has to remember and learn the locations of several different visual patterns. The test has aspects of a delayed response procedure and a conditional learning task, because the subject initially has to remember the location of a single stimulus over a short delay, and then the locations of up to 8 different stimuli within a maximum of 10 trials.

Delayed response performance and conditional associative learning are impaired both in patients (Petrides, 1985; Freedman and Oscar-Berman, 1986*a*) and monkeys (Petrides, 1982) with frontal lobe damage. Freedman and Oscar-Berman (1986*b*) extended the use of the classical delayed response procedure to make comparisons between two groups of PD patients, with and without dementia and a group of DAT patients, finding deficits in the patients with dementia. Conditional learning has been found to be deficient in PD patients without dementia (Canavan and Passingham, 1985; Gotham *et al.*, 1986; Gotham *et al.*, 1988), although no direct comparison has yet been made with DAT patients.

Using the tests described above, it has been possible to define different profiles of impairment in various aspects of visual memory between Parkinson's disease and DAT, which may be useful for differentiating the cognitive deficits in these two conditions and for the elucidation of neural mechanisms in comparative studies with animals.

## SUBJECTS

### *Dementia of Alzheimer type (DAT)*

All 12 patients attended the Maudsley Hospital and all except for 1 were seen on an outpatient basis through the Memory Clinic. The exception was seen as an inpatient during her assessment period. Patients were assessed and diagnosed by a consultant psychiatrist (R.L.) in concordance with a second psychiatrist (M.P.) as having DAT following the criteria outlined for 'probable Alzheimer's disease' by McKhann *et al.* (1984). All patients were considered to be in the early stages of the disease and fell in stage 1 of the Clinical Dementia Rating Scale, as defined by Hughes *et al.* (1982). To determine the diagnosis, patients were first seen by a psychiatrist on attending the Memory Clinic, where they received a semistructured clinical interview and a physical examination (Philpot and Levy, 1987).

Following a physical examination, which included the testing of visual acuity with Snellen cards, blood was taken for laboratory investigations. An unenhanced CT brain scan was then performed to determine the extent of brain atrophy, and to exclude other forms of dementia, especially multi-infarct dementia. The 12 patients (6 males and 6 females) included in the study were then seen on a subsequent visit by a clinical psychologist for detailed neuropsychological assessment, including the tests described in more detail below. Further details of the 12 patients are shown in the Table.

TABLE. SUMMARY OF CHARACTERISTICS OF PATIENTS AND MATCHED CONTROLS (MEAN (SD) VALUES)

| *Group* | | *Age* | *Verbal IQ* | *NART IQ* | *OLT (number correct)* | *DCT (s)* |
|---|---|---|---|---|---|---|
| DAT | Patients | 72.3 (6.6) | 116.9 (27.9)† | 115.5 (10.8) | 14.9 (6.8) | 88.2 (17.3) |
| | Controls | 71.7 (5.7) | 125.0 (15.4) | 116.2 (9.4) | 40.1 (6.9)* | 78.6 (13.2) |
| MED PD | Patients | 64.2 (6.8) | 114.9 (16.4) | 112.8 (9.6) | 33.2 (8.5) | 105.6 (21.5) |
| | Controls | 65.1 (3.3) | 115.6 (15.2) | 115.6 (6.7) | 42.0 (4.2)* | 74.5 (16.8)* |
| NMED PD | Patients | 61.3 (6.3) | 111.2 (12.6) | 112.4 (9.0) | 37.5 (8.6) | 101.3 (21.0) |
| | Controls | 61.9 (6.3) | 112.8 (17.6) | 113.0 (10.3) | 40.8 (7.0) | 69.9 (10.0)* |

* Significantly different from controls ($P < 0.05$) (Student's t test). † Including 1 patient with a WAIS verbal IQ score of 62 NART = Nelson Adult Reading Test; OLT = Kendrick Object Learning Test; DCT = Kendrick Digit Copying Test.

### *Parkinson's disease*

Two groups of patients with idiopathic Parkinson's disease were formed: (1) recently diagnosed patients, early in the course of the disease, who had not yet received antiparkinsonian medication (NMED PD; n = 13, 8 male, 5 female); (2) patients generally later in the course of the disease, already receiving medication (MED PD; n = 14, 8 male, 6 female). All patients were diagnosed by a physician and the severity of the symptoms was rated using the Hoehn and Yahr scale (Hoehn and Yahr, 1967). The MED PD group was all drawn from outpatients of the Department of Neurology, Addenbrooke's Hospital, Cambridge. Patients forming the NMED group were drawn from several sources because of the difficulty of obtaining parkinsonian patients prior to medication. They were referred by consultant neurologists at the following hospitals: Addenbrooke's Hospital, Cambridge; Bedford District Hospital; Leeds Royal Infirmary; Norfolk and Norwich Hospital; and the Hammersmith Hospital, London. In the NMED PD group, 7 subjects were at stage 1 on the Hoehn and Yahr scale, 4 at stage 2 and 2 subjects at stage 3. The mean duration of symptoms at the time of testing in the NMED PD group was 1.7 yrs (range 0.5–4.5). In the MED PD group, 2 subjects were at Hoehn and Yahr stage 1, 3 at stage 2, and 9 at stage 3. The mean duration of symptoms was 7.6 yrs (range 3-16). None of the patients tested had a psychiatric disorder and none was diagnosed as demented. None of the patients exhibited a gross loss of visual acuity when visual function was assessed (corrected with spectacles, if necessary) during the course of clinical examination. All but 2 patients were right-handed. In the MED PD group, all patients were receiving an L-DOPA preparation at the time of testing. Four patients were also receiving anticholinergic medication. Further details of the patients are shown in the Table.

### *Control subjects*

Control subjects were matched with patients by age and verbal IQ, and where possible by sex. Control subjects were volunteers drawn from three areas· Newcastle-upon-Tyne (North-East Old Age Research Panel), Cambridgeshire and London. These controls had no history of neurological or psychiatric disorder. For further details, *see* Table.

Informed consent for neuropsychological testing was obtained from all subjects.

## METHODS

### *Neuropsychological tests*

All patients and control subjects received the following tests: the Comprehension and Vocabulary subtests of the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1955), the National Adult Reading Test (Nelson, 1982), and the Object Learning Test (KOLT) and Digit Copying Test from the Kendrick Cognitive Tests for the Elderly (Kendrick, 1985).

### *Experimental computerized tests*

The subjects were tested using an Acorn BBC+ microcomputer fitted with a 14 inch Microvitec high resolution video display unit (VDU) and a Microvitec Touchtech 501 touch sensitive screen. The microcomputer controlled the generation and presentation of stimuli, visual and auditory feedback and the experimental contingencies. The location and latency of subjects' response to the touchscreen were also recorded.

The subjects sat with the VDU approximately 0.5 m in front of them and the experimenter explained that they would be required to look at the VDU screen and make responses by touching it. The memory tests were preceded by a sensorimotor test, in which the patients were trained to point accurately at the screen and assessed for this ability (only 1 subject had to be excluded because of severe motor impairment). They were then led through the series of automated tests by the experimenter who used standardized verbal instructions (a detailed protocol can be obtained from the authors, on request). Before each test there were several practice trials to make the subjects familiar with the test procedures. If the subjects required clarification of the test instructions or appeared initially to misunderstand them, standardized verbal prompts were provided by the experimenter.

*Pattern recognition.* In the STUDY phase, the subjects were presented with a series of abstract coloured visual patterns in the centre of the screen (*see* fig. 1A). Each stimulus was presented for 3 s, with no manual response being required of the subject. There were two blocks of 12 stimuli each. Five seconds after the end of each block, in the TEST phase, the subjects were required to choose between the pattern they had already seen and a novel pattern, by pointing to the former. The two choice stimuli differed in shape, but not in colour, and were simultaneously presented on the screen, positioned equidistantly to the left and right of the original location of presentation.

For both the spatial and pattern recognition tests, the order of presentation in the recognition phase was the reverse of that for the STUDY phase. An auditory tone was sounded when subjects made their responses and visual feedback was provided for correct and incorrect responses. This feedback was in the form of green ticks or red crosses superimposed on the stimulus chosen by the subject.

*Spatial recognition.* In the STUDY phase, the subjects were shown a sequence of open white squares at 5 different positions on the screen, with each square being presented at each location for 3 s. No manual response was required of the subject in this phase. There were 4 blocks of 5 stimuli each and no location was used more than once as a stimulus in the STUDY phase. Five seconds after the end of each block, in the TEST phase, the subject was presented with 2 white squares in different locations, 1 of which had been previously used and 1 of which had not. The subject had to indicate which of the 2 locations had been previously used by pointing to the appropriate white square.

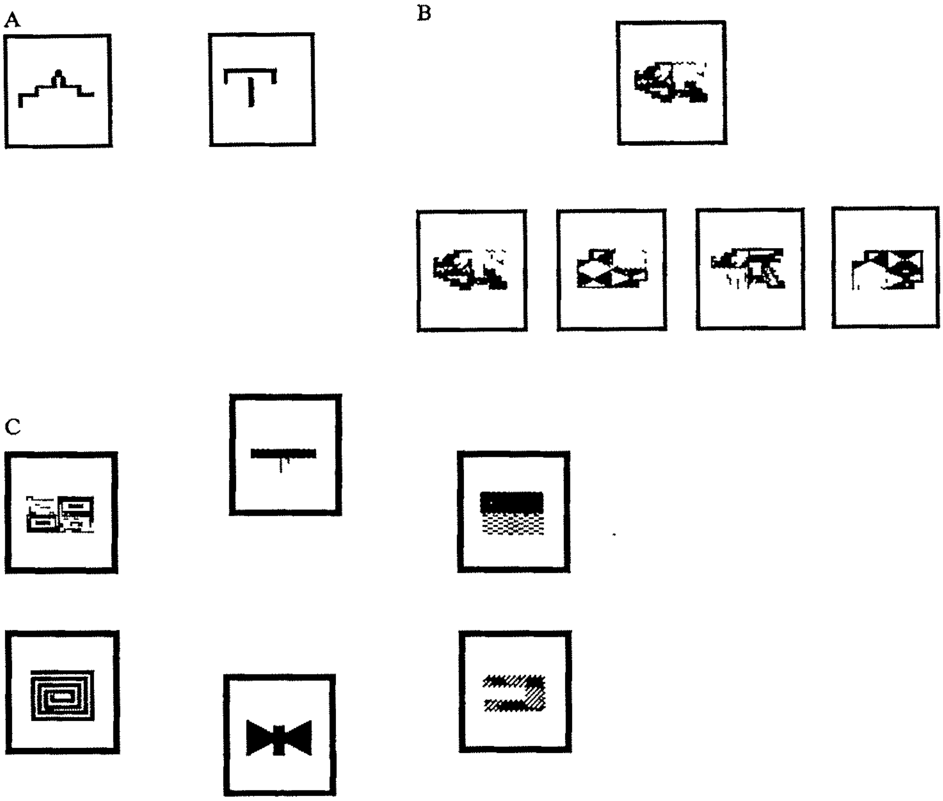

FIG. 1. Examples of stimuli used and their arrangement on the screen of the video display monitor for (A) the pattern recognition test, (B) the matching-to-sample test and (C) the delayed response and conditional learning test. In the latter example, for the purposes of illustration, the stimuli are all shown together. The spatial arrangement of the 'boxes' containing the stimuli is approximate and not drawn exactly to scale.

The measure used for both the Pattern and Spatial Recognition tests was the Number correct, calculated from 24 trials (2 blocks of 12 each) for pattern recognition, and for 20 trials (4 blocks of 5 each) for spatial recognition The data were analysed as raw scores, but presented as percentage correct scores.

*Matching-to-sample* (*MTS*). This was a test of both simultaneous and delayed matching-to-sample. Cued by a brief auditory tone, the subjects were shown a complex abstract pattern (the sample) in the centre of the screen in the STUDY phase and required to match it to 1 of 4 other choice patterns shown underneath in the TEST phase. Each visual pattern comprised 4 subelements, each of a different colour, and pilot studies with normal subjects showed that they could not easily be given a verbal label (*see* fig. 1B). One of the choice patterns was identical to the sample, 1 was a novel distractor pattern, 1 had the shape of the sample and the colours of the distractor and the fourth had the colours of the sample and the shape of the distractor The novel distractor was very different from the sample; as a whole stimulus, it matched neither in colour nor in shape. No pattern was used more than once, the stimuli were thus trial-unique. Subjects were given differential visual and auditory feedback for correct or incorrect responses (green ticks or red crosses, superimposed on the choice stimuli and different sounding auditory tones). If incorrect, they had to continue to choose until they were correct.

The sequence of trials was as follows. Initially, simultaneous matching-to-sample was tested. In this section of the test, the sample stimulus was presented in the centre of the screen, and the subject had to point to the stimulus which matched it from the 4 choices presented below (*see* fig. 1B) Following verbal instruction, 2 practice trials were given, followed by 5 test trials. The next section of the test was delayed matching-to-sample (DMTS), in which the sample stimulus appeared in the same central location as before, but for only 4 5 s. After it had disappeared, the 4 matching stimuli were presented, as before. The delays for the onset of the matching stimuli were 0, 4, 8 and 16 s. At 0 s delay the sample disappeared from the screen and the matching stimuli were then immediately presented. There were 8 trials at 0 s of which 3 were practice and 5 were test trials, followed by 5 test trials at 4 s, 5 at 8 s and 5 at 16 s This ascending sequence of delays was deliberately chosen to avoid possible effects of surprise seen in pilot studies with dementing subjects, when short delays followed long ones. In order to control for possible order effects (e g., of practice or of fatigue), an additional block of 5 trials with 0 s delay was administered after the block at 16 s.

Only data for the initial choice were used for calculating the number of correct responses. (1) Simultaneous MTS. Number correct (out of 5 trials). (2) Delayed MTS. Number correct (separately for 0, 4, 8 and 16 s, each out of 5 trials). (3) Delayed MTS. Retest at 0 s delay, out of 5 trials. Each of these scores was analysed as the number of correct responses and presented as a percentage. (4) Error analysis. Initial incorrect responses were categorized according to which distractor had been chosen (shape, colour, or unrelated).

### *Delayed response; conditional visuospatial associative learning*

In this test, the subject was required to learn a set of pattern-location associations varying in number from 1 to 8. The test started at a very simple level and became more complex with later sets of stimuli. Initially, 6 filled white squares arranged in a ring around the margins of the VDU screen were presented and described to the subjects as boxes that could be opened. In the STUDY phase, the boxes were 'opened' (the white square became unfilled) successively for 3 s, in a randomized order, 1 of them containing an abstract visual pattern. These differed in nature from those used in the pattern recognition and MTS tests (*see* fig. 1C for examples) and no pattern was used for more than one set. Immediately after the last box had been opened, in the TEST phase, the pattern was shown in the middle of the screen and the subject was required to point to the box in which it had previously been presented. If the choice was incorrect, the boxes were all successively reopened (for 2 s each, in a randomized sequence) as a 'reminder' STUDY phase, before the subject was again tested. No other feedback was provided until the subject placed the stimulus correctly, when the VDU screen showed the message 'All correct', before the next set was presented. The first set constituted a practice trial to ensure that the subject understood the task requirements.

After 3 correct sets with a single pattern, the number of patterns was increased to 2 (2 sets), 3 (2 sets), 6 (1 set) and then to 8 (1 set), which necessitated 2 additional white boxes. No pattern was used more than once. The order of presentation of the patterns in the TEST phase was random with respect to that of the STUDY phase Subjects were allowed to choose each box more than once on a given trial. For each set of stimuli, the subject had up to a maximum of 10 trials to remember correctly the locations of all of the patterns in the set. Failure to do this resulted in the test being automatically terminated by the computer.

The main measures used were as follows. (1) Memory Score. The number of stimuli correctly located on the first trial of each set of stimuli was recorded. An overall memory score was computed by summing these scores over all sets of stimuli attempted. (2) Learning. This was assessed in several ways, most simply as the incidence of subjects in each group reaching each set of stimuli, but also as the numbers of trials taken or errors made in reaching a criterion of all correct for each set of stimuli. Composite learning scores were derived by summing the trials and errors to criterion over all sets of stimuli, allotting for: (i) trials—the maximum score of 10 to those sets which were not attempted by subjects because of failure at an earlier stage; and (ii) errors—the score obtained by the worst subject attempting a set, for those subjects not reaching that set.

Learning curves were also constructed for those subjects reaching sets with 6 or 8 stimuli, using the number correct on each trial (and also the number consistently correct from the final trial backwards, although this method gave generally similar results). Maximum scores for number correct were assigned to all subsequent trials on which subjects attained all correct scores.

The entire test battery generally took between 45 and 50 min, the MTS and delayed response components occupying the bulk of the time. Subjects seldom complained of fatigue and generally appeared interested in the tests and motivated to do well. When asked subsequently, a large majority of the subjects stated that they had enjoyed the tests. Several spontaneously expressed their preference for this mode of assessment over the pencil and paper tests they had previously experienced.

### *Design and statistical procedures*

The design employed was to define a group of subjects as comprising the patients and controls for a particular condition, i.e., NMED PD, MED PD and DAT. For those analyses not involving a second factor such as time or trials (in DMTS and the learning component of the delayed response, respectively) two-tailed matched-pair Student's t tests were used, comparing within each group (i.e., NMED PD, MED PD, DAT) the patient with his or her matched control subject. When a second factor was involved, analysis of variance was used, in which a 'plot' consisted of each pair of subjects (patient vs control) and the significance of differences between patients and controls, and their interaction with other factors such as Trials or Delay, was tested using the within-plot factor Pair. Separate analyses involving unmatched t tests or analyses of variance led to similar results.

Likelihood ratio analysis of contingency tables was applied to data involving incidence or frequency, as described by Kullback (1959) and Robbins (1977). Briefly, this form of analysis is related to $\chi^2$, but can be used with cells of small frequency. The test statistic 2i is distributed as $\chi^2$, with (n-1) (m-1) degrees of freedom.

The intercorrelation matrix (using Spearman's rho) was computed for a number of variables from the combined (NMED and MED) PD patients ($n = 27$), including the pattern and spatial recognition choice accuracy scores, the total DMTS score (untransformed), the errors to criterion scores for the delayed response task and the total memory score for the first trial of that task, age, verbal IQ, the Hoehn and Yahr disability ratings and the duration of the disease.

## RESULTS

### *Pattern and spatial recognition*

As can be seen in fig. 2, the DAT and MED PD groups were significantly impaired in retention accuracy, relative to their matched control groups both for pattern recognition (respectively, $t(11) = 2.58$; $P < 0.05$: $t(13) = 3.82$; $P < 0.01$) and for spatial recognition (respectively, $t(11) = 3.74$; $P < 0.01$: $t(13) = 4.90$;

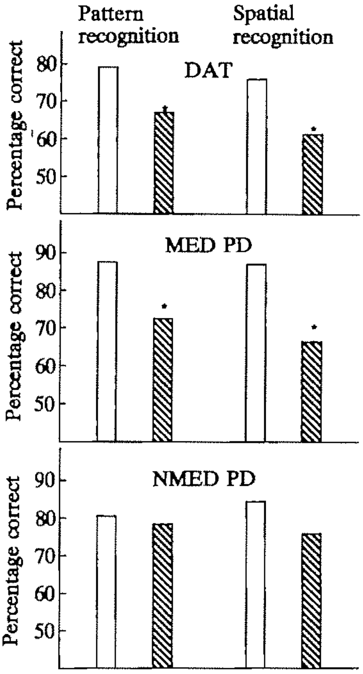

FIG. 2. Percentage retention accuracy in the tests of pattern and spatial recognition. The asterisks indicate significant differences ($P < 0.05$, or less). For this and subsequent figures, DAT = dementia of the Alzheimer type; NMED = unmedicated Parkinson's disease, early in the course of the disease; MED PD = medicated Parkinson's disease, later in the course Open areas = controls; hatched areas = patients

$P < 0.01$). As a group, the NMED PD subjects were unimpaired in both tests (pattern: t(12) = 0.44; $P > 0.05$: spatial t(12) = 1.44; $P > 0.05$).

### *Matching-to-sample*

The results for the choice accuracy measure are shown in fig. 3 for all stages of the matching-to-sample procedure. The data for simultaneous MTS and DMTS were first analysed separately using analysis of variance, and then with the DMTS scores being adjusted for the simultaneous MTS performance, using analysis of covariance. The data were all arcsin square root transformed, as recommended by Winer (1971), because of the pronounced positive skewness of the data.

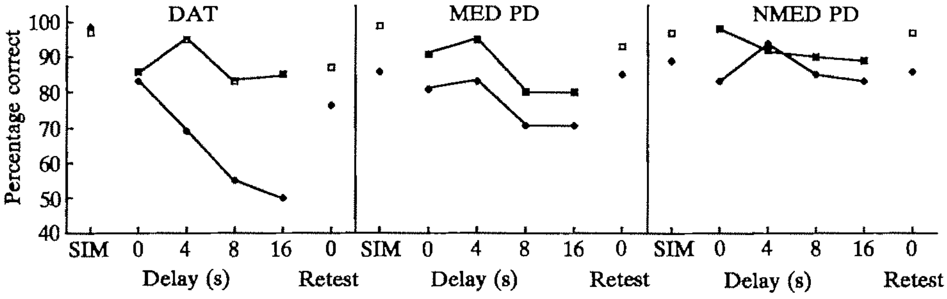

FIG 3. Percentage correct scores for simultaneous matching-to-sample (SIM), delayed matching-to-sample, at each delay, and the retest at 0 s delay. Squares = controls; diamonds = patients.

*Simultaneous MTS*. The DAT group had a similar choice accuracy score to its control group (F(1, 11) $< 1.0$; $P > 0.05$). By contrast, the NMED and MED PD groups were both significantly impaired (NMED, F(1, 12) $= 5.08$; $P < 0.05$: MED PD, F(1, 13) $= 9.31$; $P < 0.01$).

*Delayed MTS*. Fig. 3 shows that the DAT group, while showing similar performance to their controls at 0 s delay, thereafter exhibited a rapid decline in performance as a function of increasing delay, so that performance began to approach chance levels at 16 s, whereas the controls showed little decrement. There was a significant Pair × Delay interaction (F(3, 66) $= 3.19$; $P < 0.05$). Further analysis of the simple main effects showed that there was no significant effect of Delay in the DAT controls (F(3, 33) $= 2.20$; $P > 0.10$ (despite the apparent improvement in accuracy at 4 s). In contrast, the DAT patients showed a highly significant effect of Delay (F(3, 33) $= 7.04$; $P < 0.001$), with the Linear trend accounting for 94.2% of the variance (F(1, 33) $= 19.91$; $P < 0.001$). The control subjects were not at ceiling levels of performance at 0 s delay, because a post hoc t test showed the scores to be significantly less than in the simultaneous condition (t(11) $= 2.11$; $P < 0.05$, one-tailed). The mean accuracy score averaged over Delay for the controls was also significantly different from the simultaneous condition score (t(11) $= 2.87$).

By comparison, the two PD groups had different patterns of performance. The MED PD patients showed a significant decline in performance, irrespective of the delay (F(1, 13) $= 6.89$; $P < 0.05$) and the NMED patients exhibited a qualitatively similar, but not significant decline in performance (F(1, 11) $= 2.88$; $P > 0.05$). There were no significant interactions with Delay in these two groups. The deficit in the MED PD group was removed following analysis of covariance with the simultaneous MTS scores as the covariate (F(1, 13) $< 1.0$; $P > 0.05$).

*Retest at 0 s delay*. Performance in the retest at 0 s was compared with that in the first 0 s condition for the three groups of patients and controls, using analysis of variance. None of the three patient groups showed a significant difference in performance between the initial test and the retest. Although the data shown in fig. 3 indicate a slight decrement in the performance of the DAT patients retested at 0 s, compared with the initial test, this did not reach statistical significance (F(1, 22) $= 2.00$; $P > 0.05$), and nor was there an overall decrement in the performance of the DAT patients over the 2 tests (F(1, 11) $= 2.10$; $P > 0.05$). It is therefore most unlikely that fatigue or related factors could have produced the large decline in performance as a function of delay in the DAT patients.

Fig. 3 shows that the differences seen at 0 s in the MED PD patients were still apparent in the retest, although they did not quite reach significance (F(1, 13) $= 4.48$; $P < 0.10$) and there was no significant interaction with retesting (F(1, 26) $< 1.0$; $P > 0.05$). Performance generally showed a small but significant improvement across the 2 tests (F(1, 26) $= 4.59$; $P < 0.05$). For the NMED condition, this method of analysis indicated a significant overall impairment of choice accuracy in the patient group (F(1, 12) $= 5.13$; $P < 0.05$), irrespective of retesting (F(1, 24)

= 1.11; $P > 0.05$). There were no overall differences in performance between the 2 tests (F(1, 24) < 1.0; $P > 0.05$).

An analysis of types of initial errors made during the DMTS task showed that the colour distractor was chosen most often (about 59% of the total), followed by the shape distractor (34%), with rather few responses being made to the novel distractor (7%), even in the DAT group (12%). This pattern was not obviously different across the groups. Contingency table analysis of the total errors made in each group (patient and control) resulted in a $\chi^2$ value of 16.3 (10 df); $P > 0.05$.

In summary, the DAT patients and the MED and NMED groups showed different patterns of impairment in MTS. The DAT subjects were unimpaired at simultaneous MTS, but showed a steep decline as a function of delay in DMTS. By contrast, the MED PD group showed a deficit independent of delay and also in the simultaneous MTS condition. There were indications of a similar, though smaller, deficit in the NMED group.

*Delayed response and conditional visuospatial associative learning*

Progression through the various stages of the delayed response test is indicated in fig. 4. If subjects failed to attain criterion at a particular set within 10 trials, the test was terminated. Thus the figure shows the proportion of subjects failing at each stage. Only 1 control subject failed to reach criterion at all stages of the

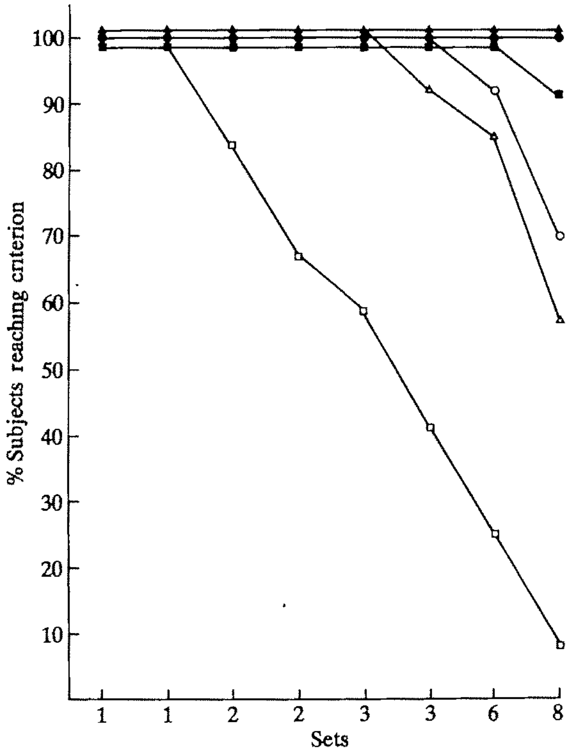

FIG. 4. Percentage of subjects attaining criterion within 10 trials for each set of stimuli in the delayed response task. Note that only 1 (DAT) control failed to reach criterion at all stages of the test. Filled symbols = controls; squares = DAT, triangles = MED PD, circles = NMED PD

test, 1 DAT control failing at 8 items. The incidence of failure in the patient groups was much higher. Only 3 of the 12 DAT patients managed to learn the 6 item set, and only 1 of these managed the 8 item set. Contingency table analysis showed that there was a significant attrition rate in the DAT patients by the second set of 2 items ($\chi^2 = 6.4$; df = 1; $P < 0.05$). There was also a significant impairment in the MED PD patients at the 8 item set which was learned completely only by 8 out of 14 patients ($\chi^2 = 9.98$; df = 1; $P < 0.01$). Four of the NMED patients (of 13) failed to learn the 8 item set, a result which also attained significance ($\chi^2 = 6.28$; df = 1; $P < 0.05$). In view of the complexity of the results, each group of subjects (patients plus controls) is now considered separately, although group mean learning curves are depicted together in fig. 5.

*DAT*. The DAT patients were severely impaired in the acquisition of the conditional visuospatial discrimination, whether the impairment was measured in terms of the total trials taken, or errors made, to criterion scores. The patients had a mean total trials score of 41.1 trials compared with their matched control scores of 15.0 trials (t(11) = 5.1; $P < 0.001$). There was clearly also a very large deficit using the total errors score, so analysis focused on the two adjusted errors

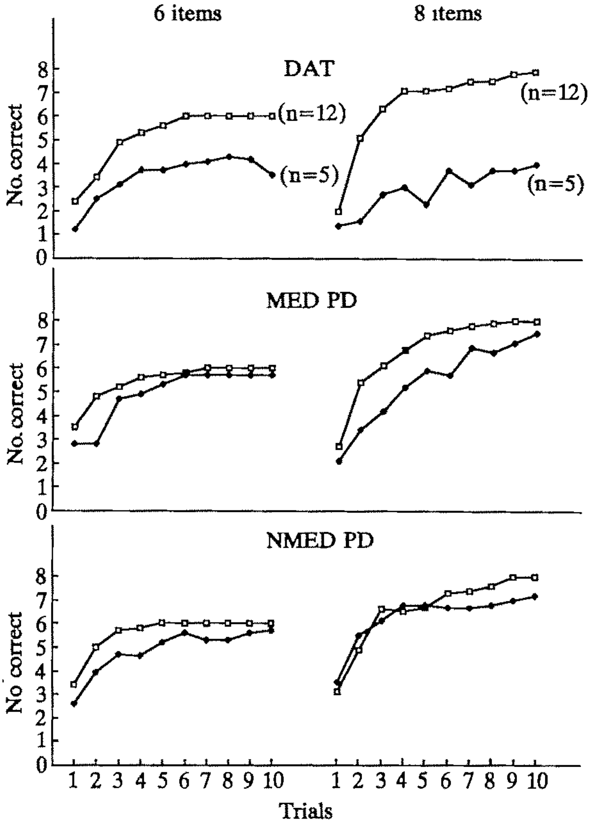

FIG 5. Group mean learning curves over 10 trials for the sets of 6 and 8 items in the delayed response task. Note that the scores shown can only be calculated from those subjects attempting these sets and that the number of subjects contributing to the mean values in the NMED and MED PD groups can be derived from the incidence of success shown in fig. 4. Squares = controls; filled diamonds = patients.

scores. When the numbers of errors between the DAT patients and their matched controls were directly compared over the same sets of the test up to and including the set on which the patient failed, the DAT group had a mean of 47.8 errors and the controls only 5.8 (t(11) = 13.6; $P < 0.01$). The large difference was not due simply to the errors made on the set on which patients failed to attain criterion, because there was also a significant difference in the incidence of errors between the two groups considering only those sets on which criterion was attained (patients mean, 11.5; controls, 2.3; t(11) = 3.71; $P < 0.01$). Thus the DAT patients were making more errors even on the sets on which they reached criterion.

Fig. 5 shows that acquisition was clearly retarded for those DAT patients attempting the sets with 6 and 8 items. No statistical analysis was attempted for the 3 DAT patients at 8 items, but for the DAT subjects at 6 items, there was a significant Pair × Trial interaction (F(9, 135) = 2.07; $P < 0.05$), which further analysis revealed to be due to inferior performance in the patients from the third trial onwards.

*MED PD*. The MED PD patients were also impaired relative to their controls: mean total trials, 20.9 vs 14.21, t(13) = 2.95: mean total errors, 46.4 vs 19.1 (t(13) = 3.22; $P < 0.001$). The respective adjusted error mean scores were 37.8 vs 17.8 (t(13) = 2.93; $P < 0.01$).

In terms of the learning curves at 6 and 8 items, the apparent performance decrement shown in fig. 5 for 6 items by the MED PD patients over all trials was not, in fact, significant (F(1, 13) = 2.66; $P > 0.05$), and there was no support for a learning deficit as shown by the lack of an interaction of Pair with Trials (F(9, 234) < 1.0; $P > 0.05$) (although the alternative index of learning, number consistently correct, did reveal a significant interaction). For 8 items the overall deficit was significant (F(1, 11) = 6.41; $P < 0.05$), but again there was no significant interaction with Trials.

*NMED PD*. Despite the significantly reduced successful attainment of criteria at the 8 item sets, none of the other differences in measures of learning or performance was significant. Thus no significant differences emerged using total trials or total errors to criterion, at least using the criterion of a two-tailed test (mean scores + SEM: total trials, patients, 17.2 + 1.8, controls, 13.5 + 0.9; t(12) = 1.99; $P > 0.05$): total errors, patients, 35.9 + 10.6, controls, 19.5 + 3.8; t(12) = 1.50; $P > 0.05$). Fig. 5 shows that there was a general tendency for the NMED patients also to be worse than their controls at both 6 and 8 items, although this was not significant in either case (6 items; F(1, 12) = 3.60; $P < 0.10$: 8 items; F(1, 12) < 1.0; $P > 0.05$). In summary, it appears that whereas a proportion of the NMED patients were impaired in learning the pattern-location associations for the 8 item set, this failure was not representative of the group as a whole.

### *Delayed response; first trial scores*

The scores on the first trial of each set, totalled over sets, were used as measures of memory. The DAT patients were significantly worse than their matched controls on the total memory score (mean scores, patients 7.2, controls 14.3; $t(11) = 5.02$; $P < 0.001$), and also on the corrected memory score, for which the first trial scores of each DAT patient were compared directly with those of their matched controls over the sets they attempted; mean scores, patients 7.2, controls 10.1; ($t(11) = 4.84$; $P < 0.001$).

The MED PD patients were also impaired in terms of this measure of memory. The patients had a mean total score of 13.0, compared with the control score of 17.0 ($t(13) = 2.95$; $P < 0.01$). The substitution of a corrected memory score for the controls did not alter this result (control mean = 16.1; $t(13) = 2.32$; $P < 0.05$).

The NMED patients showed no impairment on the memory measure (mean scores, patients = $16.2 + 1.52$; controls $17.7 + 0.7$; $t(12) = 0.99$; $P > 0.05$).

### *Correlation analysis of PD patients*

The greatest degrees of association between ratings on the Hoehn and Yahr disability scale or duration of illness and the variables measuring cognitive performance were found for the memory score on the delayed response task. The correlation coefficients for Spearman's rho were respectively $-0.535$ and $-0.509$ (both $P < 0.001$). Of the other variables, only errors to criterion for delayed response reached significance, this being largely due to the high correlation of this variable with the memory score on the same task.

## DISCUSSION

This study has used a number of computerized tests of visual memory to compare the performance of patients with DAT and PD. Although the DAT group was more severely impaired than the medicated and nonmedicated PD groups on some of the tests used, there was evidence of equivalent or greater susceptibility of the PD groups in certain conditions.

The DAT patients showed a deficit in choice accuracy on the delayed matching-to-sample test which depended strongly upon delay. There was no impairment whatsoever in the simultaneous matching-to-sample condition, and performance at 0 s delay, where the matching stimulus immediately follows the sample, was also not significantly different from control levels, either for the initial block, or for the retest. The delay-dependent deficit seems unlikely to have been due to some artefact of scaling, as it could not be removed statistically by any transformation tried. Performance was not at ceiling level in the DAT patients and controls at the 0 s condition, as it differed significantly from that observed in the simultaneous condition. Furthermore, the PD patients (especially in the MED PD group) were not at ceiling levels of performance because they were significantly worse than their matched controls, for both the simultaneous and delayed versions of the task. The deficit in the PD group was, however, independent of delay. These considerations suggest that the delay-dependent effects of the DAT group were unlikely to have arisen from a generalized disruption of performance, or from ceiling levels of performance shown in normal controls.

The DMTS results are theoretically important for a number of reasons. First, there is an unambiguous deficit in visual short-term memory in the DAT group. Their normal performance in the simultaneous MTS version shows that they were capable of responding according to an MTS procedure and perceiving and attending to the compound stimuli used as samples. Thus their rapidly declining performance as a function of delay suggests an inability to retain the sample in STM.

Previous studies of visual short-term memory using the verbal Brown–Peterson task (e.g., Kopelman, 1985; Morris, 1986) or nonverbal tests of spatial span (Sullivan *et al.*, 1986) have all shown substantial deficits when the interval was filled with a distracting task, but, unlike the present demonstration, the deficit was mild in the absence of such a task. Furthermore, the exact interpretation of the previous results is difficult, for two reasons. First, as Morris (1986) pointed out, the impairment he found could not unambiguously be attributed to faster rates of forgetting in the DAT group, because the significant Groups × Delay interaction could have arisen from the ceiling in performance (i.e., close to 100%) in the controls and there was no statistical support for faster forgetting when the no delay condition was excluded from the analysis. Kopelman's (1985) results with the Brown–Peterson task are also equivocal in this regard. The interpretation of the data of Sullivan *et al.* (1986) would also seem to be compromised by ceiling effects in both DAT and control groups at 0 s delay, in all conditions. The second problem of interpretation arises because DAT patients have recently been shown to be impaired in those executive processes governing dual-task performance (Baddeley *et al.*, 1986) which are almost certainly implicated in some versions of the Brown–Peterson paradigm (Vallar and Baddeley, 1982). Thus the increased forgetting observed in DAT patients on the Brown–Peterson task may be due to difficulties they have in dividing their attention between remembering the material and performing the distractor task.

As it is very difficult to label the MTS patterns, it is doubtful that an impairment of verbal rehearsal underlies the delay-dependent deficits in the DAT patients. It was possible to name the four colours used in each sample, and it is of interest that errors were more prevalent for all groups in matching the shapes, rather than the colours, of the sample. However, the proportions of the different types of error were not significantly altered in the DAT patients, and so it is unlikely that they were especially deficient in this form of verbal rehearsal. Morris (1984) has also provided evidence that patients with DAT have a normal capacity to use the articulatory loop, showing that basic verbal rehearsal capacities are unimpaired in this group. It remains possible that patients with DAT are impaired in somewhat ill-defined processes of nonverbal rehearsal, as suggested by Milner (1968) for patients with damage to the right temporal lobe (*see also* the discussion in Sullivan *et al.*, 1986).

The faster forgetting of the DAT group may be restricted to short-term visual memory, as there have now been several reports of equivalent forgetting rates over longer temporal intervals after initial levels of learning in DAT patients and controls had been equated (Corkin *et al.*, 1984; Kopelman, 1985; Becker *et al.*, 1987; but *see also* Hart *et al.*, 1987). One implication of this difference in forgetting rates between primary and secondary visual memory is that the inferior performance by DAT patients in the latter reflects a deficit in memory consolidation, or transfer from short to long term memory, as previously suggested by Miller (1971).

The dissociable pattern of deficits for the PD and DAT patients is important in placing constraints on the notion of 'generalized cognitive decline' which is often applied to DAT. Whereas it is clear that DAT can profoundly affect several, perhaps independent functions, it seems that there must be some selectivity in the nature of the cognitive processes that are impaired (which is, of course, much more evident in the case of PD).

Deficits in visual matching in PD have been reported previously (e.g., Pirozzolo *et al.*, 1982), though not always independently of delay (Horne, 1971). There are several possible interpretations of the present deficit. One is that it arises from deficits in PD patients of visual sensory function (Bodis-Wollner *et al.*, 1984). Regan and Maxner (1987) recently reported an orientation-selective visual loss of contrast sensitivity of probable central origin in PD patients, which might conceivably have interfered with the perception of some of the complex patterns used in the MTS task. A loss of attention, arising for example from impaired oculomotor control in the PD patients (Bronstein and Kennard, 1985) might also have led to inefficient scanning of the sample, although in the simultaneous version of the task, at least, the presentation of the sample was not temporally limited. Furthermore, it is pertinent to note that similar eye-movement deficits have been reported to occur in patients with DAT (Hutton *et al.*, 1984), and yet the DAT patients of the present study were not impaired in simultaneous MTS. The fact that the samples were complex, varying both in colour and shape, might also implicate the impairments in attentional switching that have previously been reported in PD (e.g., Lees and Smith, 1983; Cools *et al.*, 1984; Flowers and Robertson, 1985), particularly where perceptual switching is required, as in the case of the Necker Cube (Talland, 1962).

The patients in the DAT group were also significantly impaired in two aspects of visual recognition memory for patterns, and for spatial location. It is striking that the deficits seen in patients with DAT were matched by those of the MED PD patients, though not by the NMED PD patients. The results for visual spatial and pattern recognition memory in the MED PD group contrast markedly with those reported by Flowers *et al.* (1984). The population of PD subjects described by Flowers *et al.* was similar in terms of their age, medication and disease severity, and so it seems likely that the discrepancy is due to differences in the details of the tests themselves. Flowers *et al.* (1984) did not include a specific test of recognition of spatial location, but did employ tests of recognition of drawings of objects, of slides of abstract paintings and 'nonsense' histograms. Recognition memory performance for histograms appeared to be close to floor levels, whereas for objects it was close to ceiling levels, which in either case would have obscured possible differences between the patients and controls.

However, a more likely explanation for the discrepancy is the interval between the presentation of the stimuli and the retention test. Sagar (1984) has found in PD patients that recognition of the content of visual material was impaired at short (1–3 s), but not at longer intervals after presentation. Exactly the same result was found in the present MTS task for NMED PD patients (fig. 3). Matching was impaired with no delay, and with 0 s delay either at the beginning or at the end of the test sequence (when both were analysed together). However, when the delay was longer, the deficit disappeared. In the Flowers *et al.* (1984) study, the 'immediate' test of retention in fact occurred following a 1 min delay, which would have obscured most of the differences between the PD patients and controls, although in the case of object recognition the difference between the groups was apparently significant.

Sagar (1984) interpreted his results as supporting the clinical concept of bradyphrenia, in that memory in PD was poor soon after registration of material, but improved after an interval. A similar interpretation of the present results may be possible, although the impairment even when there was no delay (i.e., in the simultaneous MTS condition) may be more compatible with a form of perceptual or attentional deficit.

One further aspect of the poor mnemonic performance of the MED PD subjects needs to be stressed because these subjects were significantly impaired on the Kendrick Object Learning Test which involves verbal free recall rather than recognition memory. It has been suggested that tests such as free recall are more sensitive to the memory impairment in Parkinson's disease because they involve a greater degree of 'active' or 'effortful' processing (Flowers *et al.*, 1984; Weingartner *et al.*, 1984). However, the present study shows that the MED PD patients are clearly impaired on the two tests of recognition memory, a finding that does not support a strong distinction between recognition and recall performance in Parkinson's disease.

The DAT patients had substantial impairments in both the memory (first trial scores) and in the conditional learning components of the delayed response task which were generally greater than those shown in the PD patients. Many of the latter, however, were also impaired. Some DAT patients were unable to learn the locations of 2 or 3 different patterns in the 10 attempts allowed, and only 1 subject was able to learn the location of 8 patterns. In comparison, Muramoto (1984) found that DAT patients were inferior to those with multi-infarct dementia in learning the locations of common objects, but used a selective reminding procedure and failed to employ a normal age-matched control group. Corkin (1982) also reported that DAT patients were deficient in nonverbal paired associate learning, although in her study, there was no significant deficit in the mild DAT cases most comparable with the present sample. In addition, the form of learning in the Corkin (1982) study was nonspatial, involving stimulus-stimulus associations, rather than the stimulus-location (or stimulus-motor response) associations of the present study.

The finding of impairments in visuospatial conditional learning in the medicated PD group adds to other reports of deficits involving stimulus-stimulus conditional learning (e.g., Canavan and Passingham, 1985; Gotham *et al.*, 1986, 1988). Extrapolating from the findings of Petrides (1985) for patients with frontal lobe damage, these results are compatible with the 'frontal' hypothesis of PD. Almost one-third of the NMED PD group were also unable to learn the task at the 8 item stage, whereas all of their matched controls were able to do so.

The MED PD patients were also impaired in the first trial memory component of the delayed response task. Performance on this task for all PD patients correlated more highly with the clinical assessment of motor disability (as measured by the Hoehn and Yahr scale) than any other variable (including measures of speed of performance not presented here). Therefore, there appears to be some correlation between the motor symptoms of PD and an aspect of cognitive function which cannot obviously result from motor disability. The correlation with memory in the delayed response task was quite specific, because there was little correlation between the Hoehn and Yahr ratings and other indices of mnemonic performance. This specificity may be because of the visuospatial nature of the delayed response task. In support of this, Mortimer *et al.* (1982) reported a correlation between the degree of bradykinesia (but not tremor) and visuospatial deficit, and Taylor *et al.* (1986) reported that two out of the three cognitive deficits they found in patients with PD, including delayed spatial recognition performance, correlated with the severity of the disease.

In summary, this comparison between DAT and PD in tests of visual memory and learning has shown equivalent deficits in some cases (pattern and spatial recognition), more severe deficits for DAT in others (delayed response memory and conditional learning) and qualitatively different impairments for MTS. The comparison is somewhat complicated by the possible effects of age, severity of disease and medication, but is facilitated by the provision of age-matched control groups, the doubly dissociable effects found between the PD and DAT groups for MTS and, in some cases, the comparison between the MED and NMED PD groups. Recent results have shown that medication might have produced some of the present impairments in cognitive performance in the MED PD group (Gotham *et al.*, 1986, 1988). A reanalysis of the results for the spatial and pattern recognition tests (not shown) indicated that the deficits were not due to the anticholinergic medication that 4 of the subjects were receiving, but could still have been due to L-DOPA treatment. However, it is more difficult to explain all of the deficits seen in the MTS and conditional learning tests as being due to medication, as qualitatively similar and significant, though smaller, effects were seen in the NMED PD group. The smaller size of these impairments is to be expected, as the

NMED PD patients were also generally earlier in the course of the disease than the MED PD group.

The present results are also important for extrapolating results from the extensive literature on the effects of focal brain lesions and neuropharmacological manipulations on cognitive processes in nonhuman primates. As described in the Introduction, the present pattern recognition and MTS tasks resemble those that have been used to define the neural substrates of visual memory (Mishkin, 1982). The monkey tasks used by Mishkin differed from the present ones largely in their use of objects rather than two-dimensional stimuli and a nonmatching, rather than matching, rule, but were similar in not including a distractor task during the delay interval and in using trial-unique stimuli.

In monkeys, visual recognition and DMTS (or DNMTS) performance has been disrupted by lesions which include damage to the inferotemporal cortex (Mishkin, 1982; Sahgal and Iversen, 1978), hippocampus, amygdala, various combined lesions of these structures and also of structures they innervate, such as the anterior thalamic nucleus and the mediodorsal nucleus of the thalamus (Mishkin, 1982). These deficits, like those of the present study, are generally delay-dependent. Thus it is possible that the severe deficit in visual short-term memory shown by the DAT patients in this study reflects dysfunction of temporal lobe structures, a possibility consistent with the pattern of neuropathological and neurochemical changes seen in this condition (for review, *see* Tomlinson, 1984).

Neurotoxic lesions of the nucleus basalis of Meynert have also recently been shown to impair DMTS and serial recognition performance in rhesus monkeys, if they are challenged with the anticholinergic drug scopolamine (Aigner *et al.*, 1987). This implication of the cortical cholinergic projections in visual recognition memory may be relevant to the deficits seen in both DAT and PD, in view of some of the neuropathological and neurochemical evidence (Edwardson *et al.*, 1985).

Impairments in MTS performance in monkeys have also been seen following lesions of ventral portions of the prefrontal cortex (Passingham, 1975; Mishkin and Manning, 1978), although the forms of the task used in those studies, unlike those used by Mishkin (1982) and this experiment, did not use trial-unique stimuli. Of particular importance for the present study is that the prefrontal lesions impaired matching performance both at short delays and in a simultaneous condition (Passingham, 1975). Therefore, it is possible that the similar deficit seen in the PD patients in the present paper might result from frontal lobe dysfunction.

In contrast to MTS, conditional learning is susceptible to lesions of the posterior part of the dorsolateral prefrontal cortex in monkeys and this deficit has been suggested to contribute to some of the other effects of such lesions such as delayed alternation (Petrides, 1982). In Freedman and Oscar-Berman's (1986*b*) study of delayed alternation and delayed response, both demented PD and DAT patients were equally poor at delayed response, but only the DAT group was significantly impaired at delayed alternation. However, the two tasks may have differed in sensitivity because there were no errors in the delayed response task in control subjects or PD patients without dementia. The possible lack of sensitivity in the delayed response task may have resulted from the use of a verbal mediating strategy, a major problem when adapting animal tests for human subjects. In order to overcome this problem in the present study it was found necessary to make the task more complicated by requiring the subject to remember the locations of several stimuli, rather than the one required in the classical delayed response paradigm. This added complexity led to clear deficits in the delayed response memory component of our visuospatial conditional learning task for both the MED PD (who were not diagnosed as dementing) and DAT groups, with the latter exhibiting the greater impairment. The modification also makes the present test somewhat like the spatial memory task of Smith and Milner (1981, 1984), although there are major procedural differences. Their task was sensitive to damage to the right hippocampus (Smith and Milner, 1981), but not the frontal lobe (Smith and Milner, 1984). These results are of interest in view of the deficits in conditional learning in patients with damage to either the frontal lobes or the right hippocampus found by Petrides (1985).

From both the animal and human evidence, it would seem likely that conditional learning and the spatial component of delayed response-like tasks are subserved by a neural circuit that includes frontal cortex and the hippocampal region of the temporal lobe and this is again compatible with the neuropathological evidence in DAT (Tomlinson, 1984; Edwardson *et al.*, 1985). The frontal cortex sends topographical projections to the caudate nucleus (Johnson *et al.*, 1968) which is also implicated in the performance of frontal lobe-type tasks (Divac *et al.*, 1967), including delayed response in monkeys (Battig *et al.*, 1960). This is of particular interest in the present study in view of the significant relationship of the delayed response, first trial memory scores with the clinical index of disability in the PD patients and may support the hypotheses of Taylor *et al.* (1986) and Gotham *et al.* (1988) that parallel circuitry within the striatum is responsible for some of the cognitive, as well as the motor, symptoms of PD.

In conclusion, the comparative approach used in this study for delineating deficits in visual memory and learning in DAT and PD, has gained, not only from the comparison between the different patient groups, but also from a careful comparison with evidence from neuropsychological studies of subhuman primates.

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# RECORDING OF MOVEMENT-RELATED POTENTIALS FROM SCALP AND CORTEX IN MAN

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## SUMMARY

Movement-related cortical potentials (MRPs) were recorded from scalp electrodes in 8 normal volunteers and from chronically implanted subdural electrodes in 7 patients who were being evaluated for surgical treatment of epilepsy. From subdural electrodes, a clearly defined, extremely localized slow negative potential preceding the voluntary movement of the middle finger (Bereitschaftspotential, BP) was recorded in the contralateral and ipsilateral hand sensorimotor areas. The negative slope (NS′) began approximately 250 to 400 ms before EMG onset and was recorded exclusively from the contralateral hand sensorimotor area. Both BP and NS′ were maximum in the hand motor area. Although a negative slope was recorded also from the supplementary motor area, whether that particular slope corresponded to BP or NS′, or both, could not be determined.

Three kinds of progressively steeper negative potentials starting around the onset of the EMG were identified: (1) the 'hand motor potentials' which were seen in the contralateral hand motor area and started immediately before EMG onset and peaked 130 ± 32 ms after EMG onset; (2) the 'hand somatosensory potentials' seen in the contralateral hand somatosensory area which started simultaneously or immediately after the EMG onset; and (3) the 'vicinity potentials' seen in the immediate surroundings of the contralateral hand area and which started after the EMG onset. The 'hand motor potentials' had the highest amplitude. From these findings, we concluded that bilateral hand sensorimotor areas and the supplementary motor area participate in the 'preparation' of movements, but that mainly the contralateral cortex generates the discharges necessary to produce the actual movement.

## INTRODUCTION

Potentials occurring immediately preceding and following a voluntary movement are defined as movement-related cortical potentials (MRPs). Cortical potentials related to 'voluntary' movement are of interest because they may help to elucidate the neural mechanisms participating in movement preparation, movement initiation and motor control. MRPs have been studied extensively with scalp recordings (Kornhuber and Deecke, 1965; Vaughan *et al.*, 1968; Deecke *et al.*, 1969; Shibasaki *et al.*, 1975, 1980; Shibasaki, 1982; Barrett *et al.*, 1986*a*, *b*)

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and also with intracranial recordings (Arezzo and Vaughan, 1975, 1980; Groll-Knapp *et al.*, 1977; Gemba *et al.*, 1979; Hashimoto *et al.*, 1979; Sasaki *et al.*, 1979; Ganglberger *et al.*, 1980; Johnson, 1980; Pieper *et al.*, 1980; Lee *et al.*, 1986). In spite of these studies, there still is considerable controversy regarding the exact description and origin of MRPs. Previous direct intracranial recordings of MRPs have not shed significant light on this controversy because of technical factors. To average MRPs successfully, the patient has to be well relaxed and artefacts from eye movements and nonstereotyped movements should ideally be excluded. Most previous intracranial studies were performed acutely in the operating theatre which does not provide optimal conditions. In our studies, the patients were studied outside the theatre, which gave us enough time to average a large number of trials and to evaluate the reproducibility of the trials. In addition, extensive storage capabilities allowed the application of computer-assisted techniques (Barrett *et al.*, 1985) which permitted elimination of artefact-contaminated movements.

This study presents MRPs recorded from up to 28 electrodes placed over the scalp in 8 healthy volunteers and MRPs recorded from 21 to 38 chronically implanted subdural electrodes in 7 patients with intractable epilepsy.

## MATERIAL AND METHODS

### *Material*

The subjects comprised 8 normal volunteers (mean age 29 yrs, range 24 to 38) and 7 patients (mean age 22 yrs, range 12 to 38) undergoing operation for intractable epilepsy. Informed consent was obtained from all patients following procedures approved by our Institutional Review Board.

In normal volunteers, 28 silver-silver chloride cup electrodes were fixed on the scalp with collodion, using the 10–20 system plus extra electrodes placed in the midpoint between standard 10–20 system electrodes.

In 7 patients a plate of subdural electrodes was implanted over the left perirolandic area to map both (1) the extent of the epileptogenic focus and (2) the function of cortex surrounding the epileptogenic focus (Lueders *et al.*, 1982, 1987; Morris *et al.*, 1984) (fig. 1). The electrode plate consisted of 64 stainless steel electrodes divided in 8 rows of 8 electrodes each. Case 4 had electrodes implanted over the left supplementary motor area (fig. 1). The electrode plate consisted of 14 stainless steel electrodes divided in 3 rows of 4 or 5 electrodes each. Each electrode was 3 mm in diameter and the centre-to-centre interelectrode distance was 1 cm. A detailed description of the subdural electrodes and the functional tests used to define the functional significance of the cortex underlying the electrodes can be found elsewhere (Hahn and Lüders, 1987; Lüders *et al*, 1987).

### *Cortical stimulation*

To map cortical function in patients, electrical current was applied to each electrode at varying intensities either to elicit a movement, elicit a sensation or to test for interference with ongoing motor tasks or higher cortical functions. The stimulus consisted of 5 s trains of alternating polarity square-wave pulses, 0.3 ms in duration with a regular repetition rate of 50 Hz. At each electrode, the initial stimulus intensity was 1 mA, with gradual 1 mA increments until a patient experienced symptoms or signs, the cortical after-discharge threshold was reached, or a maximum of 15 mA was reached.

### *Recording technique*

Recordings in normal volunteers were made from 28 scalp electrodes using the 10–20 system, plus extra electrodes placed in the midpoint between standard 10–20 system electrodes. Recordings in patients were made simultaneously from 21–38 subdural electrodes and from 5 silver-silver chloride cup electrodes placed over the scalp at Fz, C3, Cz, C4 and Pz (International 10–20 system). The electro-oculogram (EOG) was recorded from an electrode placed 1.5 cm below the right outer canthus. The electromyogram (EMG) associated with finger movement was recorded with a pair of cup electrodes placed approximately 3 cm apart over the skin overlying the extensor muscle of the middle finger in the forearm.

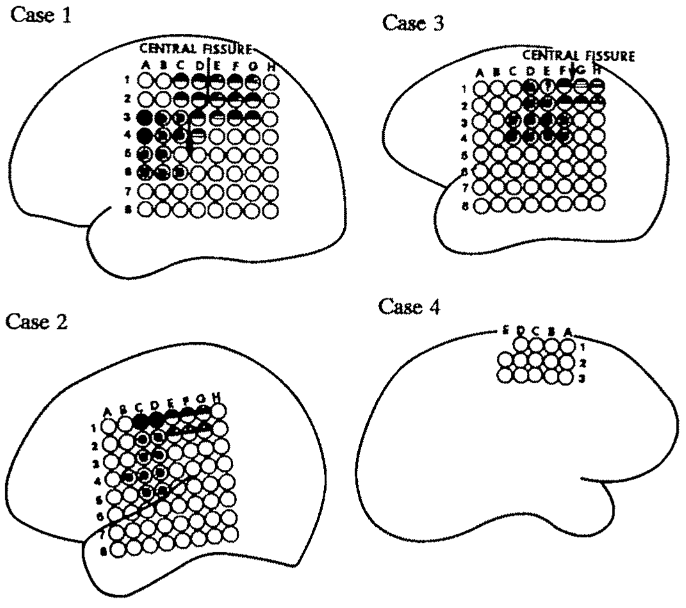

FIG. 1. Diagram of electrode nomenclature in *Cases 1 to 4* In *Cases 1 and 2*, columns of electrodes are labelled A to H from front to back. In each column, electrodes are labelled 1 to 8 from top to bottom. In *Case 2*, function of the cortex at electrode E1 could not be assessed because stimulation triggered a seizure. In *Case 4*, a plate of electrodes was implanted epidurally into the interhemispheric space over the left supplementary motor area. The electrode plate consisted of 14 stainless steel electrodes divided in 3 rows of 4 or 5 electrodes each. The diagrams shown in this figure were copied direct from lateral skull x-ray films. Stimulation at electrodes shown as empty circles produced no signs or symptoms. Language areas defined also by electrical stimulation are not included in these diagrams. Filled upper half circles = upper limb, small filled inner circles = head and face; filled circles = eyes. Black symbols = motor; hatched symbols = sensory.

All signals were led to two or three 21-channel Nihon-Koden EEG machines or a 30-channel Grass model 12 polygraph for amplification, filtering and ink-recording. All subdural and scalp electrodes and the EOG electrode were referenced to linked ear electrodes (A1+A2). The EMG was recorded between the 2 electrodes placed on the forearm. Sensitivity for the cortical recordings was 50 $\mu$V/mm and for the scalp, EOG and EMG was 7 $\mu$V/mm. The time constant for the cortical, scalp, and EOG recordings was 5 s and for the EMG was 0.03 s. The high frequency filter settings for the cortical, scalp and EOG recordings was 70 Hz and for the EMG, 1000 Hz. A 60 Hz notch filter was used in all channels. Continuous paper records were run throughout the entire experiment at a paper speed of 30 mm·s$^{-1}$.

The electrographic signals were also collected by and stored on computer for subsequent off-line analysis. The amplified and filtered signals (EEG machine output) were led to a PDP 11/44 (DEC) computer which digitized each channel at 200 samples per second. The digital data (up to 2 h) were stored on a removable computer disc.

Throughout the experiment, the subject lay on a bed with his forearm at his side, his wrist straightened and his fingers straight and relaxed. A brisk voluntary extension of the middle finger at the metacarpophalangeal joint in one hand, followed by a return to the resting position by relaxing the extended finger was used as the triggering movement. All normal volunteers were asked to move both hands. Seven patients were asked to move the right finger contralateral to the subdural plate. Three of these patients were also asked to move the finger ipsilateral to the subdural plate. Each movement was repeated voluntarily at irregular self-paced intervals exceeding 3 s. The subject was told to avoid eye movements as far as possible and that if they blinked, they had to delay for a short while before making another finger movement. He was instructed to relax and not to count during the interval between movement. A training period was given during which he was informed of his performance. Training continued until the experimenters were satisfied that the subject consistently produced brisk finger movements separated by complete finger relaxation. A recording session consisted of about 50–80 movements, and there were 5 to 7 sessions separated by a 5 min rest period in each hand.

### *Data analysis*

In order to observe the EEG activity before and after finger movement, an average EEG, time-locked to the EMG burst associated with finger movement, was prepared using special computer programs which are a modification of the methods described by Barrett *et al.* (1985). The time-locking point for each EMG burst together with EEG and EOG was entered individually at a graphic terminal. If a finger movement was not associated with a brisk EMG onset, if there was an eye movement 2 s before and 1 s after the EMG onset or if there was any other recording artefact,

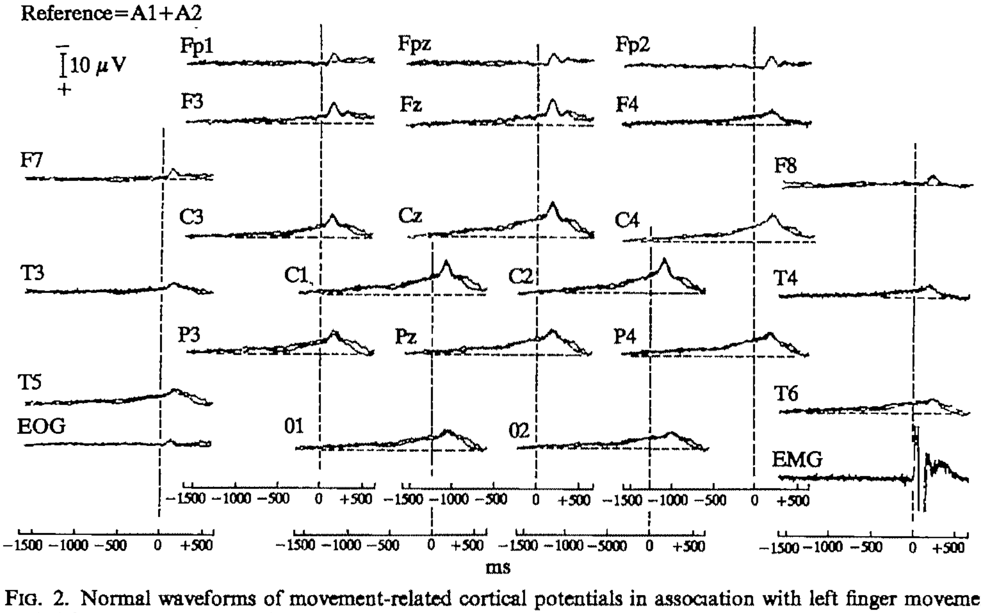

FIG. 2. Normal waveforms of movement-related cortical potentials in association with left finger movement recorded from scalp electrodes in a 38-yr-old man. The upward deflection of potentials indicates negativity (−) and downward deflection indicates positivity (+) EMG = electromyogram, EOG = electro-oculogram.

then the trial was eliminated. A total of 200 to 500 trials were averaged for each hand in this study. Two sets of EEG averages were made, each with 100 to 250 samples. EEG was averaged from 2240 ms before to 1280 ms after EMG onset. All latency and amplitude measurements were computer-assisted. Amplitude measurements were based on calibration data collected at the start of the experiment. Baseline was determined by averaging from 2240 ms to 1600 ms before EMG onset in each channel.

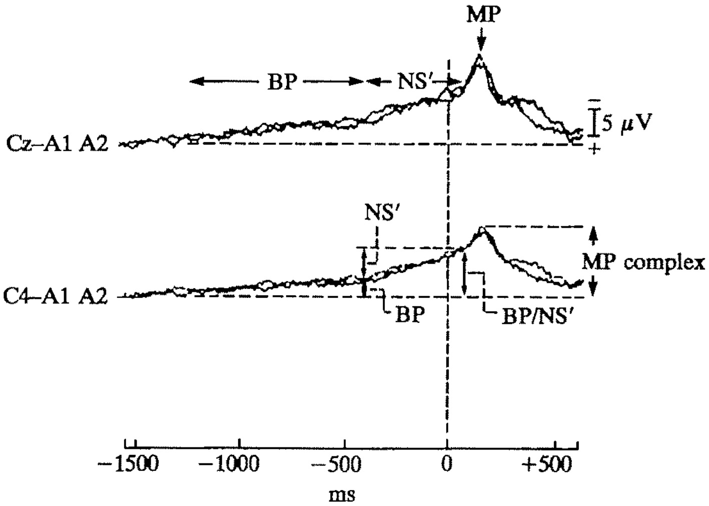

FIG 3. Terminology of each component of movement-related cortical potentials, in the same subject shown in fig. 2 in association with left finger movement recorded from scalp electrodes.

## RESULTS

### *Normal volunteers (scalp recordings)*

MRPs recorded from scalp electrodes preceding and following a left middle finger extension, obtained from a 38-yr-old man are shown in fig. 2. Fig. 3 shows 2 tracings from this normal volunteer and illustrates the nomenclature and the method used to measure latencies and amplitudes in this study. The BP, which corresponds to the previously described Bereitschaftspotential (Kornhuber and Deecke, 1965), started 1550 ms before the EMG onset and slowly increased in amplitude. Approximately 400 ms before EMG onset the slope of this negative potential became steeper (negative slope NS′—according to the terminology used by Shibasaki *et al.* (1980)). The BP was widespread but was absent in the most frontal derivations. NS′ had a less diffuse topography than the BP, occurring mainly in precentral and parietal regions. In the frontal leads, NS′ was totally absent. However, in 2 out of 8 normal volunteers, a clearly defined downward deflection was seen in the frontal derivations and simultaneously an upward deflection occurred at occipital leads. The NS′ terminated about 75 ms after EMG onset at centroparietal leads and was followed by the motor potential (MP) (Deecke and Kornhuber, 1969) which in turn had a significantly steeper slope than the NS′.This MP peaked 165 ms after EMG onset and had a widespread distribution being reflected in all leads. At Cz there was no statistical difference in latency and amplitude of the different MRP components elicited by left and right finger movements. A statistical analysis of the MRPs recorded from scalp electrode Cz elicited by right finger movements shows that the BP started 1380 ± 230 ms before EMG onset and NS′ started 380 ± 26 ms before onset. However, the onset of NS′ was clearly definable in 5 out of 8 normal volunteers. The peak of MP occurred 150 ± 22 ms after EMG onset and had an amplitude of 10.4 ± 4.8 μV. Fig 4 illustrates the MRPs in a 29-yr-old man who showed a clearly defined

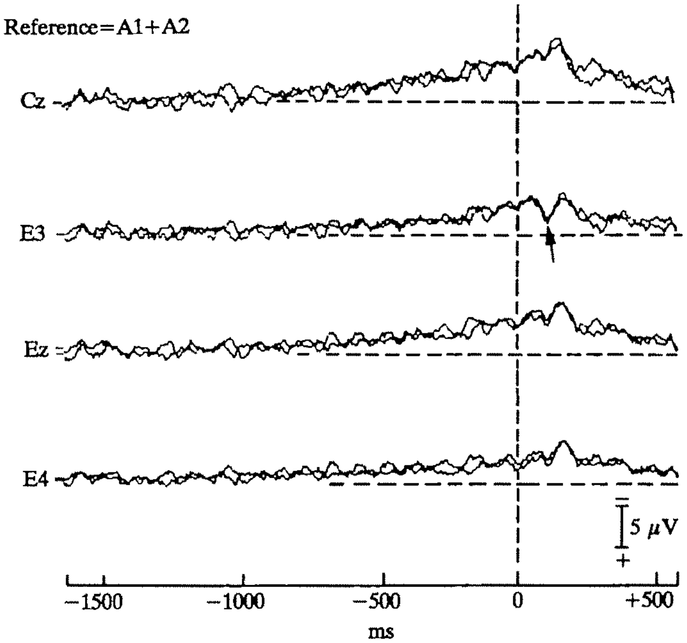

FIG. 4. Normal variation of movement-related cortical potentials in association with right finger movement recorded from scalp electrodes in a 29-yr-old man (E3, Ez, E4 = electrodes placed between international 10–20 system electrodes C3 and P3, between Cz and Pz and between C4 and P4, respectively).

positivity which peaked (marked with an arrow in fig. 4) after the EMG onset and most probably corresponds to component P−50 or a composite of P−50 and P+90 described by Shibasaki *et al.* (1980). This positivity started 90 ms after EMG onset and peaked 120 ms after EMG onset and was followed by MP. A clearly defined positivity was present in only 3 out of 8 normal volunteers.

Isopotential maps for each MRP component are shown in fig. 5. In these maps, each isopotential line represents a percentage of the maximum mean amplitude. The recordings obtained in 6 normal volunteers were used to calculate the isopotential lines. The BP was maximum at Cz and had a bilaterally symmetric distribution to left and right finger movements. The NS′ was maximum at C1 in association with right finger movements and at C2 in association with left finger movements. In other words, it had an asymmetric distribution with a contralateral preponderance. BP/NS′ and MP had essentially identical distributions, both being bilaterally symmetric but with a slight contralateral preponderance over the central region.

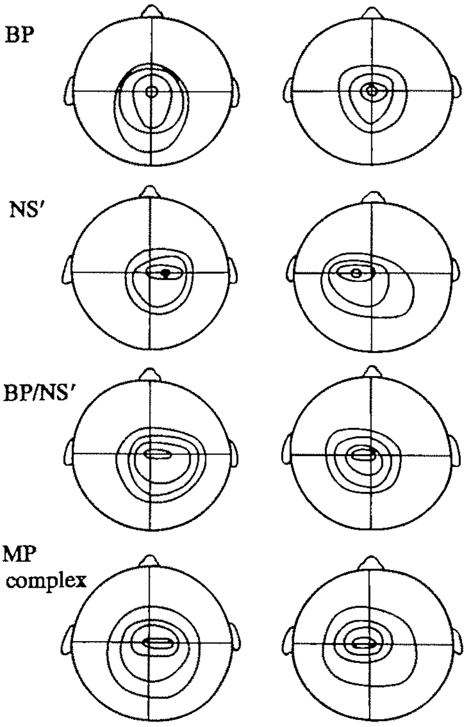

FIG 5 The isopotential mapping for each component, expressed as a percentage of the maximum mean amplitude (n = 6). *See* fig. 3 for nomenclature of components. *Left*: maps associated with left finger movement. *Right*: maps associated with right finger movement.

### *Patients*

MRPs recorded from scalp electrodes in Case 1 showed a slowly developing negativity which started about 800 ms before EMG onset at Cz, C4 and Pz (fig. 6). This corresponds to the BP of Kornhuber and Deecke (1965). Approximately 400–500 ms before EMG onset, this negative wave became steeper. This corresponds to NS′ of Shibasaki *et al.* (1980). This negativity terminated about 120 ms after EMG onset and was maximal over centroparietal and minimal over frontal electrodes. The voltage difference between the baseline and the peak of the negativity was 3.97 $\mu$V at Fz, 8.97 $\mu$V at Cz, 12.18 $\mu$V at C4 and 7.78 $\mu$V at Pz.

The MRPs from Case 1 recorded from contralateral subdural electrodes placed in an anteroposterior row crossing the central fissure at the level of the hand

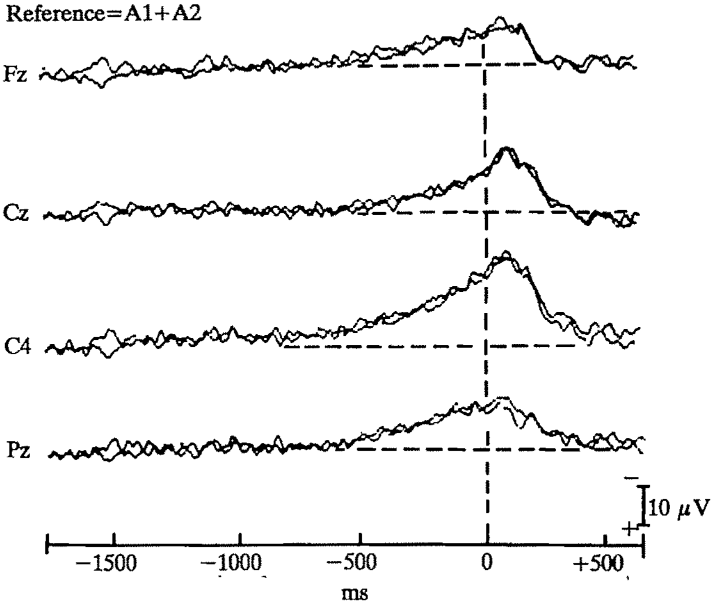

FIG. 6. Movement-related cortical potentials associated with voluntary self-paced right middle finger extension recorded from scalp electrodes in *Case 1*. Sutures prevented placement of electrodes over C3 and wound infection precautions prevented more extensive scalp distribution studies

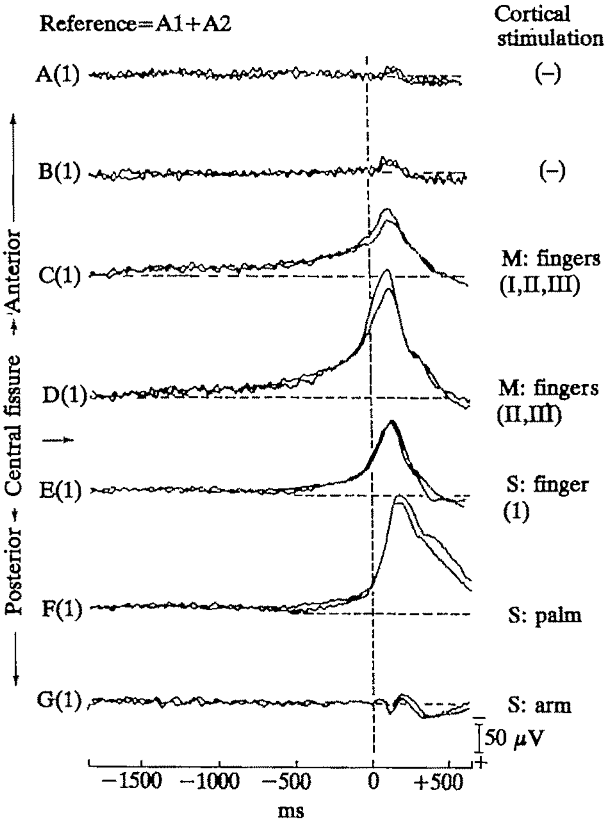

FIG. 7. Movement-related cortical potentials associated with voluntary self-paced contralateral finger extension from subdural electrodes placed in front of and behind the left central fissure in *Case 1*. S = sensory, M = motor.

motor and somatosensory area and those placed over the motor strip closest to the central fissure are shown in figs 7 and 8, respectively. A clearly defined negative potential preceding the onset of the EMG activity (BP/NS′) was recorded in an extremely localized fashion exclusively from electrodes placed in the contralateral precentral hand motor area (C1 and D1 in fig. 7, D1 and D2 in fig. 8) as well as the somatosensory area (E1 and F1 in fig. 7). BP/NS′ are seen only at C1, D1, E1 and F1 of hand motor and somatosensory area in fig. 7 and only at D1 and D2 of hand motor area in fig. 8 but disappear completely at A1, B1 and G1 outside the hand sensorimotor area in fig. 7 and at C3 and C4 of the mouth motor area in fig. 8. In other words, no potential preceding EMG onset was recorded from immediately adjacent electrodes (as close as 1 cm) placed outside the hand motor or somatosensory area. The onset of the BP occurred 1.3 s before EMG onset and was followed by the NS′ which began approximately 370 ms before EMG onset. Immediately before the EMG or at the time of EMG onset, the negative slope again became significantly steeper, giving rise to the potential which has been labelled motor potential (Deecke and Kornhuber, 1969). The MP had a slightly more widespread distribution, affecting also some electrodes immediately

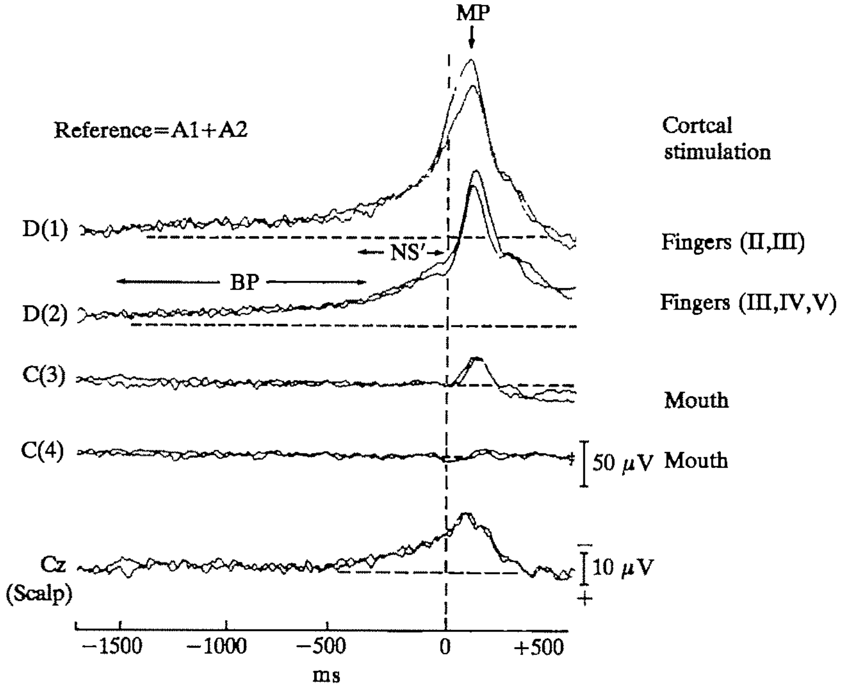

FIG. 8 Movement-related cortical potentials associated with voluntary self-paced contralateral middle finger extension from subdural electrodes placed over the left motor strip and from the vertex scalp electrode (Cz) in *Case 1.*

adjacent to the sensorimotor hand area (figs 7–11). The MP was of highest amplitude in the hand motor area where it peaked 125 ms after the EMG onset. It had, however, a longer latency in other adjacent areas (figs 7–10). Fig. 9 shows a phase reversal of the recording of the BP/NS′ and the MP

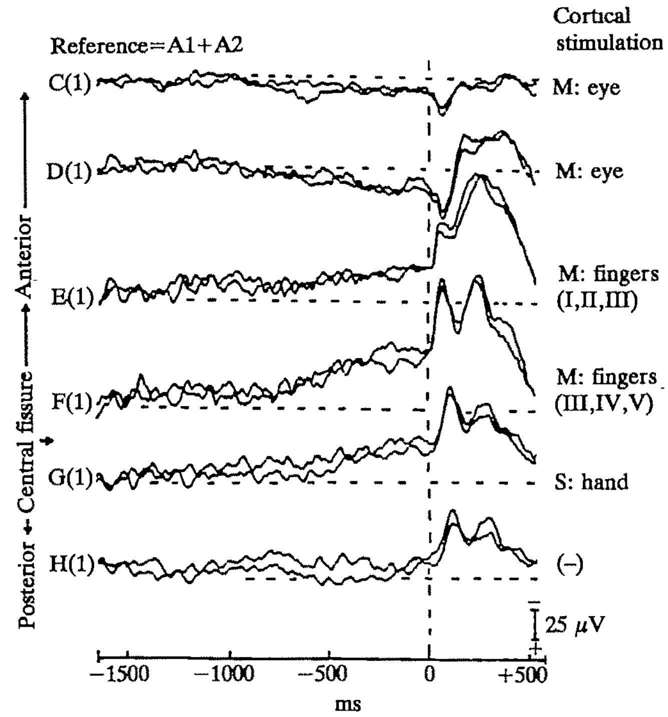

FIG. 9. Movement-related cortical potentials associated with voluntary self-paced contralateral finger extension from subdural electrodes placed in front of and behind the left central fissure in *Case 2.*

between electrodes overlying the contralateral hand motor area and electrodes placed more frontally. This phase reversal was seen only in 1 (Case 2) out of 7 patients. A statistical analysis of the MRPs recorded from subdural electrodes shows that the onset of BP and NS′ was 1240±420 ms and 315±75 ms preceding the EMG onset, respectively. The MP at the hand motor area started 47±42 ms before the EMG onset and peaked 130±32 ms after EMG onset. The MP at the hand somatosensory area started 18±24 ms and peaked 144±24 ms after EMG onset. The MP at its vicinity area started 62±8 ms and peaked 157±6 ms after the EMG onset. The MP in the hand motor area had an amplitude of 97.6 μV and was 14.0–22.6 μV higher than in the hand somato-sensory area.

Fig. 10 shows the contralateral and ipsilateral recordings from subdural electrodes placed in an anteroposterior row crossing the central fissure at the level of the hand sensorimotor area of Case 3. It demonstrates well the extremely localized nature of the BP/NS′ preceding the contralateral and the BP preceding and following the ipsilateral movements. Both BP/NS′ and MP are seen at E1 in the contralateral recordings. In contrast, NS′ and MP were either absent or of relatively low amplitude in the ipsilateral cortex. The slow negativity of approximately the same amplitude (BP) was present in contralateral and ipsilateral cortex until the onset of NS′ contralaterally. Following this, however, the ipsilateral slow negative potentials persisted and actually peaked 200 ms following EMG onset; it then slowly decreased in amplitude. These observations were consistent with those made in another 2 cases.

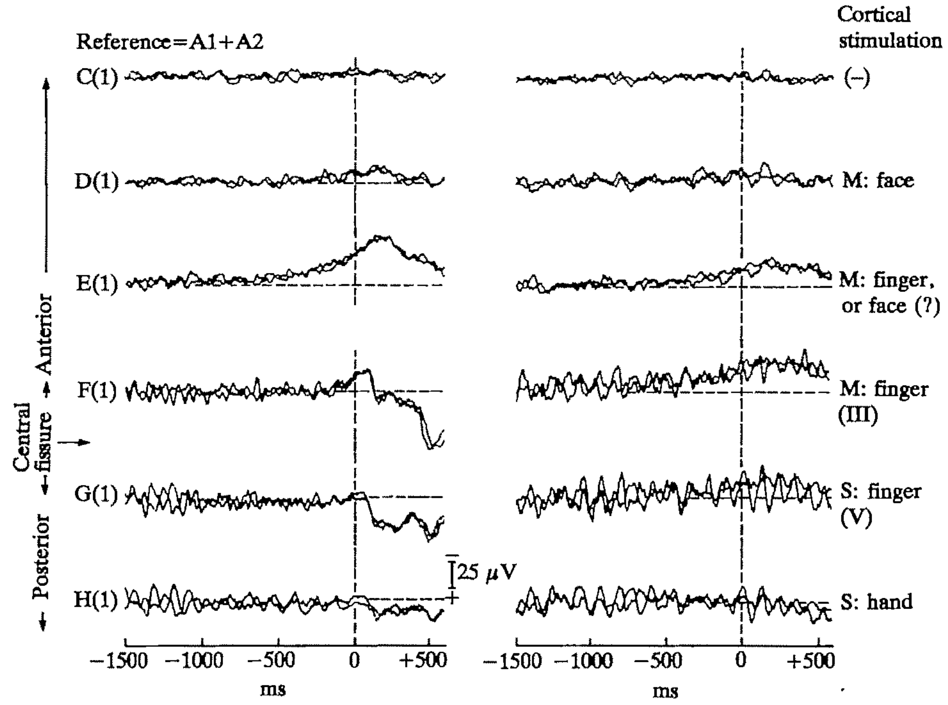

FIG. 10. Movement-related cortical potentials associated with voluntary self-paced contralateral and ipsilateral finger extension from subdural electrodes placed in an anteroposterior row crossing the left central fissure at the level of the hand motor area in *Case 3*. *Left*. Contralateral recordings to movement of right middle finger. *Right*: ipsilateral recordings to movement of left middle finger.

MRPs from electrodes placed directly over the contralateral supplementary motor area (SMA) and from scalp electrode (Cz) obtained in Case 4 (fig. 1) are shown in fig. 11. The slow negative potentials prior to movement were recorded at electrodes B1, C2, D1 and D2. Among these electrodes, the potential at D2 before the movement was the biggest and started the earliest at about 500 ms before EMG onset. This slow negative potential continued increasing with no significant change in slope up to 360 ms after EMG onset.

In a few cases, some reflection of this potential to electrodes immediately adjacent to the hand sensorimotor area was seen. However, extensive recording from 21 to 38 subdural electrodes (most of them not shown in figs 7-11) revealed that no premovement potentials could be recorded from outside the sensorimotor area or its immediate vicinity. Fig. 12 shows isopotential maps of each component obtained from subdural recordings. The BP was extremely localized to both hand sensorimotor areas. NS′ was extremely localized to the contralateral

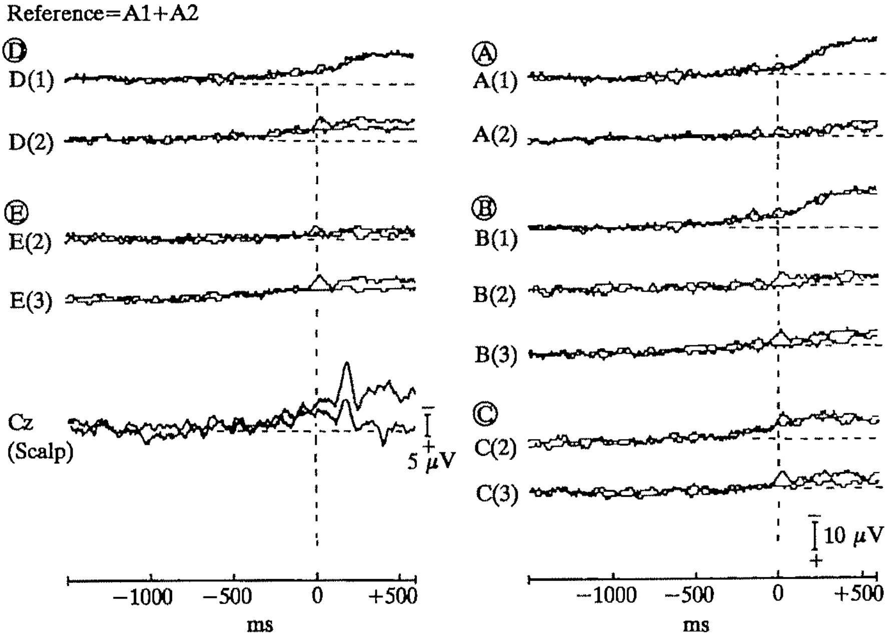

FIG. 11 Movement-related cortical potentials associated with voluntary self-paced contralateral middle finger extension recorded from epidural electrodes placed over the left supplementary motor area and from the vertex scalp electrode (Cz) in *Case 4*.

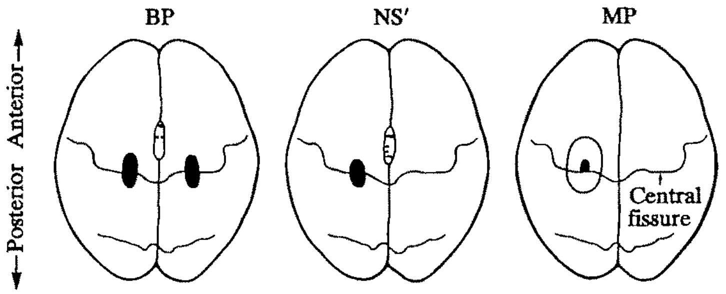

FIG. 12. Isopotential maps of BP, NS′ and MP obtained by subdural recordings viewed from top. Black ellipse in the map of BP indicates hand sensorimotor area. Black ellipse and dotted one in the map of NS′ indicate hand sensorimotor and supplementary motor area, respectively Black inner circle in the map of MP indicates hand motor area.

hand sensorimotor area and also to the supplementary motor area. The MP was localized to the contralateral hand and its vicinity sensorimotor area.

## DISCUSSION

These scalp and direct cortical recordings demonstrate that MRPs immediately preceding and following initiation of middle finger movement can be divided into 3 phases, namely the Bereitschaftspotential (BP), the negative slope (NS′) and the motor potential (MP).

A slowly rising negativity starting at 1 s or more before EMG onset and progressively increasing in negativity up to EMG onset has been demonstrated from scalp and subdural electrodes. This potential has been labelled the BP (Kornhuber and Deecke, 1965). It has been divided into 2 phases by Kutas and Donchin (1977) and later also by Shibasaki *et al.* (1980), who called the early part BP and the later portion NS′. In scalp recordings, the distribution of the BP was symmetric about the midline with a vertex maximum. NS′, however, showed a maximum slope at the contralateral centroparietal region in previous studies (Deecke *et al.*, 1969; Shibasaki *et al.*, 1980; Barrett *et al.*, 1986*b*) as also in these experiments. In subdural recordings, however, the BP was recorded in an extremely localized fashion exclusively from electrodes placed in the contralateral and ipsilateral hand sensorimotor areas. In subdural recordings, NS′ was also strictly localized to the contralateral sensorimotor region and could also be detected at the supplementary motor area. No NS′ or only a very low amplitude NS′ was seen in the ipsilateral sensorimotor area. These findings are in good agreement with the above-mentioned scalp recordings which demonstrated that the BP is bilaterally symmetrically distributed with a maximum at the vertex, whereas NS′ has a maximum lateralized to the contralateral cortex. Barrett *et al.* (1986*a*) reported an intermediate shift (IS) between the BP and NS′. In these subdural recordings, no clearly defined IS was seen. However, it is possible that different BP onset times in contralateral and ipsilateral sensorimotor area determine the IS described in surface electrodes by Barrett *et al.* (1986*a*). The finding that BP and NS′, which had a widespead distribution over the scalp, were extremely localized in subdural recordings is in good agreement with recordings of somatosensory evoked potentials to median nerve stimulation which are also extremely localized in subdural recordings but, most probably due to volume conduction, have a widespread scalp distribution.

Unfortunately, no detailed scalp distribution studies could be performed simultaneously with recordings from subdural electrodes. Wound infection precaution limited the scalp electrodes we could apply to these which the electroencephalographer used in the seizure recording protocol. It is safe, however, to assume that the MRP had a normal distribution in these patients. All the patients included in this study had a normal neurological examination. It is therefore unlikely that brain function related to voluntary movement was abnormal. In addition, the skull defect would have given us a distorted distribution of MRP even if detailed correlation studies would have been possible.

It was also interesting to observe that the BP and NS′ were negative at almost all electrodes, suggesting that they were primarily generated as bipoles perpendicular to the cortical surface. However, scalp recordings in 2 normal volunteers showed a clear negative BP and NS′ at 01 and 02 and simultaneous positive deflections at frontopolar electrodes. Also, subdural recordings of 1 out of 7 patients showed a phase reversal of BP, NS′ and MP between electrodes overlying the hand motor area and electrodes placed more frontally. These findings suggest that the BP, NS′ and MP are usually generated by vertical bipoles but in selected cases may also be produced by a horizontal bipole (most probably within the rolandic fissure) with the negative pole pointing posteriorly and the positive pole pointing anteriorly. This was in contrast to the primary somatosensory evoked potentials which always showed a clear phase reversal between postrolandic and prerolandic cortical areas (Broughton, 1967, Lueders *et al.* 1983).

There are no previous intracranial recordings that permit precise definition of the distribution of slow negative potentials. For example, in the studies of Arezzo and Vaughan (1980) only N2 (85–110 ms before the initiation of the movement) is clearly localizable to the hand motor area. This potential, however, corresponds by latency criteria to the later part of NS′ or MP. The earlier potential labelled N1 by Arezzo and Vaughan (1980) is too variable to map its distribution. In clear contradiction with our results, Arezzo and Vaughan (1980) concluded from their studies that there was no BP preceding ipsilateral movements. Only Hashimoto *et al.* (1979) succeeded in recording a slow potential before the ipsilateral movements in unanaesthetized freely moving monkeys with the electrodes implanted chronically in the surface and in the depth of the cortex. It is worthwhile noticing, however, that in their figures this ipsilateral potential was only poorly defined.

There is extensive evidence in the experimental literature supporting our results that the BP is generated in the bilateral hand sensorimotor area whereas NS′ is generated mainly in the contralateral sensorimotor and supplementary motor area. The discharge rate of neurons in the contralateral motor cortex increases by several hundred milliseconds before movement initiation in monkeys (Schmidt *et al.*, 1974; Evarts and Tanji, 1976) and cats (Neafsey *et al.*, 1978). Experimental evidence also indicates that the hand sensory area participates in the ‘preparation’ of movements. Murray and Coulter (1981) demonstrated that the postcentral cortex also contains pyramidal neurons. In trained monkeys, Pieper *et al.* (1980) and Johnson (1980) reported on postrolandic potentials preceding voluntary movement and Fromm and Evarts (1982) showed with microelectrode recordings that the neurons not only of the contralateral prerolandic hand area but also of the postrolandic hand area increase their firing rate 150 ms before onset of the EMG. Finally, there is also evidence in the literature indicating that the ipsilateral cortical hand area becomes activated preceding finger or hand movements.

Goldring and Ratcheson (1972) showed in humans that before and during simple hand movements a small number of neurons in the ipsilateral motor hand area became active. Evarts (1966) also demonstrated that a few ipsilateral pyramidal tract neurons in monkeys became active before the movements even if a greater number of them were activated before contralateral movements. He further showed that these units were related to movement of the ipsilateral wrist but not to contralateral movement. These findings could explain our observation that the premovement potentials to ipsilateral and contralateral finger movement had greatly overlapping but still slightly different distributions. Reports on the activity of the supplementary motor cortex are scarce. Brinkman and Porter (1979) reported that approximately 250 ms before the action potential of muscle producing the movement, there was an increase of neuronal firing in the motor area.

The PMP (premotion positivity) or P−50, described in scalp recordings by Deecke *et al.* (1969) and Shibasaki *et al.* (1980), was also evident in some of our scalp recordings. According to Shibasaki *et al.* (1975, 1980), P−50 is a small, asymmetric potential with ipsilateral preponderance present in about 60% of the cases and determined by a positive 'inhibitory' deflection in the ipsilateral cortex. Deecke *et al.* (1976) hypothesized that PMP might reflect cortical activity (motor command) related to the movement initiation because of its short and relatively constant firing relationship with EMG onset (80–90 ms). However, in our subdural recordings, no positive potentials with a similar latency were recorded. These findings support the assumption that P−50 is only a reflection of the onset of a new negative potential (the motor potential) on top of the BP/NS′ which has reached a plateau or begun to decrease.

The MP component was first defined by Deecke and Kornhuber (1969), being a negativity beginning just before movement onset and peaking just after. This potential was localized to the precentral region contralateral to movement and was best recorded by a bipolar pair of electrodes over the contralateral and ipsilateral precentral scalp. Shibasaki *et al.* (1980) identified their highly localized N−10 as being equivalent to this MP. Arezzo and Vaughan (1980) reported the N2 component in both man and monkey, which began between 50 and 100 ms before movement and was maximal in amplitude overlying the contralateral precentral gyrus. In the present study, the MP was seen only in the contralateral cortex. The MP clearly started first and was most prominent in the middle finger motor area. The MP following EMG onset had a significantly more widespread distribution than the BP/NS′ or than the MP immediately preceding EMG onset. From subdural recordings the MP can be subdivided according to its localization into 3 negative components. The 'hand motor potential', which started immediately before movement, had relatively the highest amplitude, reached its negative peak first, and by definition was restricted to the contralateral hand motor area. This potential most probably corresponds to the localized MP of Deecke *et al.* (1969), the N2 component of Arezzo and Vaughan (1980) or the N−10 of Shibasaki *et al.* (1980). The second component was the 'hand somatosensory potential' which started simultaneously or immediately after the movement onset, peaked slightly later than the 'hand motor potential' and by definition was restricted to the contralateral hand somatosensory area. Finally, there was a 'vicinity potential' which started after movement onset and peaked later than the other two potentials. It was seen at subdural electrodes immediately surrounding the hand sensorimotor area. This potential may correspond to the widespread N+50 of Shibasaki *et al.* (1980).

The MP following EMG onset is most probably generated by various mechanisms occurring simultaneously. On one side, we still have the potentials related to movement generation which most probably are expressed primarily by the 'hand motor potential'. In addition, however, the 'MP' following EMG onset is due to sensory feedback which we know primarily involves the postrolandic cortex but to a certain degree also affects the prerolandic cortex (Albe-Fessard and Liebeskind, 1966; Goldring and Ratcheson, 1972; Asanuma and Fernandez, 1974). It is unlikely, however, that the post-EMG onset 'MP' is only the expression of sensory feedback. This is clearly supported by the observation of Fromm and Evarts (1982) that postrolandic nonpyramidal tract neurons in areas 3a, 1, 2 and 5 start discharging simultaneously with EMG onset.

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# WORLDWIDE INCIDENCE OF PRIMARY NERVOUS SYSTEM NEOPLASMS

## GEOPLASMS GEOGRAPHICAL, RACIAL AND SEX DIFFERENCES, 1960-1977

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## SUMMARY

International and interregional comparisons of average annual age-adjusted incidence rates for primary tumours of the nervous system showed marked variations. The highest rates were observed in those areas having high socioeconomic levels In communities with multiple racial groups the highest rates were in Caucasians. Migrant populations retained rates close to those found in the country of origin. The majority of populations showed modest increases only while about one-third showed a decrease in the incidence rates during a period of approximately 15 years. Overall, there was a male excess. It is suggested that differences in medical practices (including availability of specialist expertise), diagnostic facilities and individual registry practices account for some of the variations observed. However, the possible aetiological roles of genetic, racial, hormonal and environmental factors need to be evaluated to explain the consistently higher incidence rates in Caucasians and in males of all races.

## INTRODUCTION

Until comparatively recently, reports dealing with the frequency of primary neoplasms of the nervous system were based on the experience of individual clinicians or specialized hospitals. While providing valuable descriptions on the clinical features, pathology and treatment for these tumours, these earlier reports had no information on their occurrence and distribution in well-defined population groups. Moreover, such reports inevitably reflected a selection bias inherent in a clinic or hospital series. Population studies reduce these biases. While such investigations (Brewis *et al.*, 1966; Cohen and Modan, 1968; Gudmundsson, 1970; Leibowitz *et al.*, 1971; Maroun and Jacob, 1973; Schoenberg *et al.*, 1976; Barker *et al.*, 1976; Annegers *et al.*, 1981) have been especially informative about specific geographical regions, the data accumulated in each region could not, in most cases, be compared with those from another region because incidence rates were not age-adjusted to a common standard. In addition, some centres restricted their surveys to intracranial tumours (Cohen and Modan, 1968; Maroun and Jacob, 1973; Schoenberg *et al.*, 1976; Annegers *et al.*, 1981) while others included all

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tumours of the nervous system. The most comprehensive study to date analysed all intracranial tumours, primary and secondary, based on a probability sample of inpatients in 157 US hospitals (Walker *et al.*, 1985).

There has been a considerable lack of information about geographical, racial or ethnic variation in the frequency of primary tumours of the nervous system. Still less is known about time trends in the occurrence of these tumours. Yet this type of information is useful in formulating any aetiological hypothesis. Neoplasms of the nervous system are uncommon diseases and unless observations are made on large populations, of the order of several millions (Doll and Cook, 1967), individual rates may be liable to fluctuations due to chance alone.

It is such considerations that prompted this study which was designed to analyse and compare average annual age-adjusted incidence rates for primary neoplasms of the nervous system for several distinct population groups in the world. Since data for some population groups were available for a number of years, it was also possible in selected instances to explore temporal trends to determine whether the recently shown increase in the mortality rates from these tumours (Bahemuka *et al.*, 1988) was reflected by similar trends in incidence rates.

## MATERIALS AND METHODS

Average annual age-specific incidence rates for primary tumours of the nervous system were obtained from tumour registry data worldwide which have been compiled periodically by the Union Internationale Contre le Cancer (UICC) since 1966 (International Union Against Cancer, 1966, 1970; International Agency for Research on Cancer, 1976, 1982). Currently such data are available for 104 distinct population groups representing 32 countries (International Agency for Research on Cancer, 1982). Some of the UICC material spans a period of approximately two decades. The incidence rates thus obtained were then age-adjusted to the 1960 US population, details of which are given in the 1970 US general population characteristics final report (US Bureau of the Census, 1972) using the direct method (Lilienfeld and Lilienfeld, 1980) to obtain meaningful international and interregional comparisons.

The seventh revision of the *International Statistical Classification of Diseases, Injuries and Causes of Death* (ICD) was used until 1968 when most of the registries then switched over to the eighth revision (World Health Organization, 1957, 1967). The rubrics for primary tumours of the nervous system used in the respective revisions of the ICD are shown in Table 1.

Some countries or centres excluded benign or unspecified tumours while others excluded either but not both. The distinction between malignant and benign was based on the histology and not on the clinical behaviour of the tumours. A minority of centres also registered tumours of the brain only. These inconsistencies have been clearly pointed out by UICC (International Union Against Cancer, 1966, 1970; International Agency for Research on Cancer, 1976, 1982). Consequently, only data on primary tumours of the nervous system based on identical rubrics were compared for this report. These factors also explain why temporal trends could only be examined in a minority of population groups.

## RESULTS

The populations listed in alphabetical order for easy reference are grouped according to major geographical regions and/or racial similarities. Tables

TABLE 1 CLASSIFICATION AND CODING OF PRIMARY NEOPLASMS OF THE NERVOUS SYSTEM

| *Histological grade* | *Sites* | *ICD code revision (WHO 1948, 1947 and 1967)* | | |
|---|---|---|---|---|
| | | *Sixth* | *Seventh* | *Eighth* |
| Malignant | Brain and other parts of the nervous system except optic nerve | 193 | 193 | 191-192 |
| Benign | Brain and other parts of the nervous system | 223 | 223 | 225* |
| Unspecified | Brain and other parts of the nervous system | 237 | 237 | 238 |

* Neurofibromatosis is coded as 743.4. ICD = *International Statistical Classification of Diseases, Injuries and Causes of Death.*

2-7, given in the Appendix, show the average annual age-adjusted incidence rates/100 000/yr for primary malignant tumours of the nervous system for 98 distinct population groups worldwide for 1958 to 1978. The corresponding populations at risk and the number of cases diagnosed during the study periods are also shown. At least 45.9% of these distinct population groups had over 1 million persons, while another 26.3% had between 0.5 and 1 million. Thus chance fluctuations in the age-specific incidence rates were minimized. The US whites had similar rates as the Canadians but the rates for the US blacks and other racial groups in the USA were smaller than those of their white counterparts (Table 2, Appendix).

The average male-to-female ratio (excluding Indians residing in Natal, South Africa and Filipinos living in Hawaii, for whom the sex ratio was grossly exaggerated by extremely low female rates of 0.3 and 0.2/100 000/yr, respectively) was about 1.3 for either primary malignant tumours alone (Tables 2-7, Appendix) or for all primary tumours of the nervous system (Table 8, Appendix). These sex ratios based on incidence data are similar to those previously observed for mortality rates (Bahemuka *et al.*, 1988).

When all primary tumours of the nervous system were considered regardless of histological type, the same geographical and ethnic/racial variations as well as the relative consistency of the sex ratio persisted (Table 8, Appendix).

Not only was there marked geographical and racial variation in the incidence of primary malignant tumours of the nervous system, but there was also intraregional variation. Different ethnic or racial groups living in the same region had markedly different incidence rates. This is best exemplified by population groups in Hawaii and Israel (Tables 2, 7, Appendix). In Israel, there were striking differences in the incidence rates between Jews born in Israel and Jews born elsewhere. There were also striking differences between Jews and non-Jews living in Israel. Three Israeli population groups (Jews born in Europe or America, all Jews, and Jews born in Israel) had the highest rates for primary malignant tumours of the nervous system in the world: 14.3, 10.7 and 9.5/100 000/yr, respectively.

In general, rates for most US (white) and Canadian populations were similar to those for the United Kingdom, France, the two German republics, Australia and New Zealand (Tables 2, 3, 4, Appendix). Rates for Denmark, Norway (urban) and Switzerland (Geneva) were intermediate between the Israeli and North American (white) rates. Most Asians residing in their mother countries, US blacks, some central European groups and South Americans had similar rates which were modestly higher than those for Indian and African populations (Tables 5, 6, Appendix). The last groups had the lowest rates in the world (Table 6, Appendix). When all the histological types were considered, Sweden had the highest rate of 10/100 000/yr (Table 8, Appendix), closely followed by Israel (Table 7, Appendix).

Of some curiosity was the finding that the incidence of primary tumours of the nervous system was similar in migrant and nonmigrant members of the three racial groups for whom data were available. For example, most Japanese, Chinese and Indians residing outside their native countries had incidence rates close to those observed for the indigenous populations of Japan (except Miyagi), China and India, respectively (Table 9, Appendix). It is not clear why the rates for Miyagi (Japan) were so low compared with other Japanese regions. The incidence rates for US blacks living in different areas of the US were generally lower than those for their white counterparts residing in the same region (Table 2, Appendix). In some areas, such as Alameda County and the San Francisco Bay area in California, blacks had rates close to those for whites but this was exceptional. Blacks in Atlanta, Georgia, USA, had much lower rates, which were close to those found in the predominantly black community of Jamaica (Tables 2, 6, Appendix). It is interesting that indigenous Africans in South Africa and Senegal had similar rates, albeit during different study periods (Table 6, Appendix).

From the 1960s to the 1970s there were modest increases in the incidence of primary malignant tumours of the nervous system in half of the population groups whose registries had followed the same coding system over the years (Table 10, Appendix). These increases ranged from 0.1 (Hawaiian natives) to 2.9 for blacks living in Alameda County, California. Decreases in rates occurred in 9 populations and ranged from 0.2 for the state of Connecticut, to 1.7 for Miyagi, Japan.

The subsequent changes after the early 1970s are also shown in Table 10 for 26 of these population groups. In general, there were minor changes in the rates for most populations during this latter period. However, large increases in rates of 4.1 for New Zealand (Maori), 2.8 for Hawaii (Hawaiian), 1.9 for Hawaii (Chinese) and a large decrease of 1.6 for Hawaii (Filipino) were the notable exceptions but since the populations at risk were relatively small, ranging from 60 000 to 250 000, chance fluctuations alone may account for this observation.

Analysis of rates for all primary tumours of the nervous system regardless of tumour type also showed similar changes (increases in most population groups but also decreases in a few) over time for 15 population groups. Countries racially similar and located in the same broad geographical area such as Norway, Denmark and Finland had remarkably similar incidence rates and temporal trends (Table 11, Appendix).

## DISCUSSION

This study documented marked geographical and racial/ethnic variations in the incidence rates for primary neoplasms of the nervous system. The more socioeconomically developed countries had higher average annual age-adjusted rates for either sex than the less-developed nations (Tables 2–8, Appendix). Similar variations have previously been observed for mortality rates for these neoplasms (Goldberg and Kurland, 1962; Velema and Walker, 1987; Bahemuka *et al.*, 1988). The modest but consistent male excess found in this study is also similar to that reported in the mortality study (Bahemuka *et al.*, 1988).

For white populations in Western Europe, North America, Australia and New Zealand, the average annual age-adjusted incidence rates/100 000/yr for all primary tumours of the nervous system varied between 3.8 in Los Angeles, California (Spanish/Latin) to 10.0 for Sweden as noted in Table 8, Appendix). This range is similar to that recently observed for the mortality rates of these tumours in 30 countries for 1967 to 1973 (Bahemuka *et al.*, 1988). The close agreement of the mortality and incidence rates of primary tumours of the nervous system may be a reflection of a high case-fatality ratio of these tumours.

In contrast to the increases in mortality of more than 40% in the majority of countries between 1958 and 1973 (Bahemuka *et al.*, 1988) incidence rates increased modestly and even then, in only about 60% of the populations. Increases of over 15% were observed in only about one-third of the populations. About one-third of the registries showed a decrease; overall, slightly less than 10% had no change in the frequency of primary tumours of the nervous system between early 1960s and mid-1970s (Tables 10, 11, Appendix). The reason for the consistent decrease in incidence rates of all primary tumours of the nervous system in Israel is not clear (Table 11, Appendix).

Four population groups, Alameda County, California (blacks), New Zealand (Maori), Hawaii (Hawaiian) and Hawaii (Chinese) showed exceptionally high increases (in the incidence rates) of 2.9, 4.1, 2.8 and 1.9, respectively (Table 10, Appendix). It is not certain whether this can be wholly explained by the fact that the populations at risk were relatively small. In the case of New Zealand (Maori), the situation is further complicated by the fact that the Maori rates for either sex were similar to those observed in Caucasians who generally have much higher rates than non-Caucasians (Tables 2, 3, 4, Appendix). Moreover, the New Zealand non-Maoris who are mostly Caucasian only showed a slight increase (0.3) during the same period (Table 3, Appendix). Provision of better medical facilities for and their utilization by the Maori could account for the increases in the incidence of primary tumours of the nervous system in this population. However, these findings should be interpreted with caution in view of the small size of the respective populations studied and the different durations of the study periods.

Geographical variation in the incidence of primary tumours of the nervous system may be a reflection of differences in the quality of medical practice, including availability and utility of medical facilities. Where good medical facilities, including special diagnostic services, have been well established for several years as, for example, in some Western countries, the incidence rates were not only higher than elsewhere, but remained relatively stable or changed only slightly over the years (Tables 10, 11, Appendix).

The improved medical services for the elderly in whom the age-specific rates of primary tumours of the nervous system are highest (Percy *et al.*, 1972) partly explain the higher rates generally found in socioeconomically advanced societies. It is also likely that such countries have better organized registries for data collection and coding. These factors and possibly a higher autopsy rate in such areas would improve case ascertainment.

The importance of conditions related to better case ascertainment and associated with the socioeconomic level of a country cannot be overemphasized. However, it is possible that genetic and environmental factors, including different occupational hazards, also contribute to the geographical variation in the incidence of primary tumours of the nervous system. That the Japanese, Chinese and the Indians living outside their countries have similar incidence rates to those of their compatriots living in the mother countries (Table 9, Appendix) supports the genetic hypothesis.

It is of interest to note that an analysis of 16311 cases of confirmed primary central nervous system tumours in a US medical centre showed that glioma was significantly more frequent in Caucasians than in blacks (Fan *et al.*, 1977). In that same series, meningioma and nerve sheath tumours were marginally more frequent in blacks. It is worth noting that peak frequencies for astrocytoma differed in the two races, tending to be earlier for the blacks than for the whites. Analyses of hospital cases from Nigeria, Central and Southern African regions have shown that meningioma forms a relatively high proportion of brain tumours (Froman and Lipschitz, 1970; Levy, 1973; Odeku *et al.*, 1973). Indeed, it was twice as common as glioma among the Africans of the Transvaal region of South Africa (Froman and Lipschitz, 1970). Similarly, Levy (1973) found that in a large series collected from three multiracial countries (Malawi, Zambia and Zimbabwe), meningioma formed a much higher percentage in the African than in the white patient. All these factors suggest the importance of genetic susceptibility in the development of primary tumours of the nervous system.

The finding of a lower incidence rate of glioma in large urban areas than in rural areas, at least in south-west England, further raises the possibility of environmental and occupational factors in the aetiology of some primary tumours of the nervous system (Barker *et al.*, 1976).

The case of Israeli Jews having different incidence rates depending on where they were born (Tables 7, 8, Appendix) strengthens the argument that not all the variation observed is due to access to medical care. Indeed, observations among Jewish immigrants to Israel suggest the possibility of different risk factors present in childhood in the countries of origin or that the critical exposure occurred before immigration from the country of birth. Thus it is interesting that the incidence of primary tumours of the nervous system in Israel has declined in recent years (Table 11, Appendix).

The difference in the incidence rates between the two sexes demonstrated in this study suggests that hormonal factors may be important in the aetiology of at least some primary tumours of the nervous system. In the specific case of meningioma, the observation that meningioma occurs more frequently in females than in males (Schoenberg *et al.*, 1976) tends to enlarge during pregnancy (Michelsen and New, 1969) and is in some cases associated with carcinoma of the female breast (Schoenberg *et al.*, 1975) further strengthens this hypothesis. Furthermore, there is an increase in œstrogen receptor protein in some cases of intracranial meningioma (Donnell *et al.*, 1979). Whether or not there are any other specific hormonal abnormalities associated with other types of primary tumours of the nervous system is still unknown.

In conclusion, the highest rates were observed in Israel. Different Israeli immigrant groups had different rates which were highest for those born in North America or Europe. In general, Caucasian races had high rates compared with other races. The Indian and African groups had the lowest rates in the world. Male rates were higher than female rates in most population groups. Migrant groups had similar rates to those found in their countries of origin. There were no striking increases for the majority of population groups from early 1960s to mid-1970s.

The observed differences in the incidence rates for primary tumours of the nervous system among different population groups, races and sexes may not be completely artefactual. Instead, they suggest a possible role of environmental, genetic and hormonal factors in the aetiology of these neoplasms.

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# APPENDIX

TABLE 2. AVERAGE ANNUAL AGE-ADJUSTED INCIDENCE RATES/100 000 POPULATION/YR FOR PRIMARY MALIGNANT TUMOURS OF THE NERVOUS SYSTEM FOR 38 CANADIAN AND US POPULATION GROUPS, 1960–1977

| Country | Region (racial group) | Time period | No. of cases | Population at risk (in millions) | Incidence rates | | | Male:Female ratio |
|---|---|---|---|---|---|---|---|---|
| | | | | | Males | Females | Total | |
| Canada | Alberta | 1963–1966 | 246 | 1.44 | 5.6 | 3.7 | 4.7 | 1.5 |
| Canada | Alberta | 1973–1977 | 433 | 1.78 | 6.6 | 4.2 | 5.4 | 1.6 |
| Canada | British Columbia | 1973–1977 | 660 | 2.43 | 6.3 | 4.9 | 5.6 | 1.3 |
| Canada | Manitoba | 1963–1966 | 307 | 0.96 | 8.6 | 7.9 | 8.3 | 1.1 |
| Canada | Manitoba | 1973–1977 | 299 | 1.01 | 6.9 | 5.3 | 6.1 | 1.3 |
| Canada | New Brunswick | 1965–1966 | 60 | 0.62 | 6.0 | 4.2 | 5.1 | 1.4 |
| Canada | Newfoundland | 1963–1966 | 77 | 0.49 | 4.7 | 4.5 | 4.6 | 1.0 |
| Canada | Newfoundland | 1973–1977 | 120 | 0.56 | 6.3 | 3.3 | 4.8 | 1.9 |
| Canada | NW Territories | 1973–1977 | 15 | 0.06 | 6.8 | 5.4 | 7.0 | 1.3 |
| Canada | Ontario | 1973–1977 | 1218 | 7.6 | 6.9 | 4.6 | 5.7 | 1.5 |
| Canada | Quebec | 1963–1966 | 1141 | 5.62 | 6.7 | 4.6 | 5.6 | 1.5 |
| Canada | Quebec | 1973–1977 | 1545 | 6.18 | 6.2 | 4.8 | 5.5 | 1.3 |
| Canada | Saskatchewan | 1963–1966 | 159 | 0.95 | 4.7 | 4.5 | 4.6 | 1.0 |
| Canada | Saskatchewan | 1973–1977 | 241 | 0.91 | 6.2 | 4.5 | 5.4 | 1.4 |
| USA | Atlanta, Georgia (black) | 1975–1977 | 25 | 0.36 | 2.7 | 2.4 | 2.6 | 1.1 |
| USA | Atlanta Georgia (white) | 1975–1977 | 209 | 1.17 | 8.5 | 5.6 | 6.7 | 1.5 |
| USA | California, Alameda County (black) | 1960–1964 | 14 | 0.12 | 2.6 | 1.7 | 2.1 | 1.5 |
| USA | California, Alameda County (black) | 1973–1977 | 43 | 0.18 | 6.2 | 4.4 | 5.3 | 1.4 |
| USA | California, Alameda County (white) | 1960–1964 | 197 | 0.80 | 5.6 | 4.1 | 4.8 | 1.4 |
| USA | California, Alameda County (white) | 1973–1977 | 257 | 0.84 | 6.9 | 5.9 | 6.4 | 1.2 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| USA | Connecticut | 1963-1965 | 476 | 2.77 | 5.8 | 5.3 | 5.6 | 1.1 |
| USA | Connecticut | 1973-1977 | 983 | 3.14 | 7.8 | 4.9 | 6.2 | 1.6 |
| USA | Detroit, Michigan (black) | 1973-1977 | 134 | 0.81 | 4.4 | 2.9 | 3.6 | 1.5 |
| USA | Detroit, Michigan (white) | 1973-1977 | 918 | 3.32 | 6.8 | 4.7 | 5.6 | 1.4 |
| USA | Hawaii (Caucasian) | 1960-1964 | 40 | 0.20 | 6.4 | 2.6 | 4.6 | 2.5 |
| USA | Hawaii (Caucasian) | 1973-1977 | 67 | 0.27 | 8.8 | 3.7 | 6.3 | 2.4 |
| USA | Hawaii (Chinese) | 1960-1964 | 5 | 0.04 | 1.8 | 3.4 | 2.5 | 0.5 |
| USA | Hawaii (Chinese) | 1973-1977 | 12 | 0.06 | 3.1 | 5.8 | 4.4 | 0.5 |
| USA | Hawaii (Filipino) | 1960-1964 | 10 | 0.07 | 3.0 | 4.3 | 3.4 | 0.7 |
| USA | Hawaii (Filipino) | 1973-1977 | 11 | 0.12 | 2.9 | 0.2 | 1.7 | 14.5 |
| USA | Hawaii (Hawaiian) | 1960-1964 | 13 | 0.10 | 2.3 | 3.7 | 3.0 | 0.6 |
| USA | Hawaii (Hawaiian) | 1973-1977 | 32 | 0.16 | 6.4 | 5.8 | 5.9 | 1.1 |
| USA | Hawaii (Japanese) | 1960-1964 | 20 | 0.20 | 3.0 | 1.3 | 2.2 | 2.3 |
| USA | Hawaii (Japanese) | 1973-1977 | 27 | 0.24 | 2.1 | 2.2 | 2.1 | 1.0 |
| USA | Iowa | 1973-1977 | 834 | 2.86 | 6.9 | 5.6 | 5.8 | 1.2 |
| USA | Nevada | 1959-1966 | 104 | 0.37 | 4.0 | 3.1 | 3.6 | 1.3 |
| USA | New Mexico (American Indian) | 1973-1977 | 9 | 0.09 | 4.3 | 1.2 | 2.7 | 3.6 |
| USA | New Mexico (Hispanic) | 1973-1977 | 62 | 0.44 | 4.6 | 2.3 | 3.4 | 2.0 |
| USA | New Mexico (white) | 1973-1977 | 176 | 0.59 | 8.1 | 4.2 | 6.1 | 1.9 |
| USA | New Orleans, Louisiana (black) | 1974-1977 | 54 | 0.34 | 4.8 | 4.1 | 4.4 | 1.2 |
| USA | New Orleans, Louisiana (white) | 1974-1977 | 167 | 0.68 | 7.8 | 4.6 | 6.1 | 1.7 |
| USA | NY State excluding NY City | 1973-1977 | 2837 | 10.54 | 6.4 | 4.3 | 5.3 | 1.5 |
| USA | Puerto Rico (black) | 1964-1966 | 132 | 2.64 | 2.4 | 1.4 | 1.9 | 1.7 |
| USA | Puerto Rico (black) | 1973-1977 | 310 | 3.13 | 2.6 | 2.0 | 2.3 | 1.3 |
| USA | San Francisco Bay (black) | 1973-1977 | 77 | 0.38 | 5.7 | 3.9 | 4.7 | 1.5 |
| USA | San Francisco Bay (Chinese) | 1973-1977 | 17 | 0.10 | 2.5 | 3.9 | 3.2 | 0.6 |
| USA | San Francisco Bay (Japanese) | 1973-1977 | 4 | 0.04 | 2.3 | 2.3 | 2.2 | 1.0 |
| USA | San Francisco Bay (white) | 1973-1977 | 843 | 2.53 | 7.4 | 5.8 | 6.6 | 1.3 |
| USA | Seattle, Washington | 1973-1977 | 628 | 2.36 | 7.8 | 6.0 | 6.8 | 1.3 |
| USA | Texas, El-Paso (Latin) | 1960-1966 | 29 | 0.15 | 3.7 | 3.3 | 3.5 | 1.1 |
| USA | Texas, El-Paso (other than Latin) | 1960-1966 | 37 | 0.20 | 4.2 | 2.3 | 3.3 | 1.8 |
| USA | Utah | 1973-1977 | 311 | 1.20 | 6.0 | 5.6 | 5.8 | 1.0 |

TABLE 3. AVERAGE ANNUAL AGE-ADJUSTED INCIDENCE RATES/100 000 POPULATION/YR FOR PRIMARY MALIGNANT TUMOURS OF THE NERVOUS SYSTEM FOR 16 POPULATION GROUPS IN BRITAIN AND WHITE COMMONWEALTH COUNTRIES, 1962-1977*

| *Country* | *Region* | *Time period* | *No. of cases* | *Population at risk (in millions)* | *Incidence rates* | | | *Male:Female ratio* |
|---|---|---|---|---|---|---|---|---|
| | | | | | *Males* | *Females* | *Total* | |
| UK | Birmingham | 1963–1966 | 1149 | 4.91 | 5.9 | 4.6 | 5.3 | 1.3 |
| UK | Mersey | 1963–1966 | 770 | 2.82 | 6.8 | 5.6 | 6.2 | 1.2 |
| UK | Mersey | 1975–1977 | 552 | 3.15 | 6.2 | 4.2 | 5.3 | 1.5 |
| UK | Oxford | 1963–1966 | 410 | 1.77 | 6.0 | 4.2 | 5.1 | 1.4 |
| UK | Oxford | 1974–1977 | 607 | 2.20 | 7.5 | 5.4 | 6.4 | 1.4 |
| UK | Scotland | 1963–1966 | 837 | 5.20 | 3.9 | 3.5 | 3.7 | 1.1 |
| UK | Scotland East | 1973–1977 | 122 | 0.40 | 7.2 | 4.0 | 5.5 | 1.8 |
| UK | Scotland North | 1973–1977 | 47 | 0.21 | 5.6 | 3.1 | 4.3 | 1.8 |
| UK | Scotland North East | 1973–1977 | 133 | 0.48 | 5.2 | 4.9 | 5.0 | 1.1 |
| UK | Scotland South East | 1973–1977 | 465 | 1.19 | 8.6 | 6.0 | 7.2 | 1.4 |
| UK | Scotland West | 1975–1977 | 425 | 2.90 | 5.7 | 3.5 | 4.6 | 1.6 |
| UK | Sheffield | 1963–1966 | 1031 | 4.52 | 5.6 | 4.8 | 5.2 | 1.2 |
| UK | Sheffield | 1973–1977 | 980 | 4.19 | 5.3 | 3.2 | 4.2 | 1.7 |
| UK | Southwestern | 1962–1966 | 893 | 3.00 | 6.8 | 6.0 | 6.4 | 1.1 |
| UK | Trent | 1974–1976 | 642 | 4.54 | 5.1 | 3.7 | 4.3 | 1.4 |
| Australia | New South Wales | 1973–1977 | 1307 | 4.88 | 6.4 | 4.5 | 5.4 | 1.4 |
| Australia | South Australia | 1977 only | 91 | 1.28 | 9.0 | 5.0 | 7.0 | 1.8 |
| New Zealand | New Zealand (white) | 1962–1966 | 692 | 2.40 | 6.9 | 4.9 | 5.9 | 1.4 |
| New Zealand | New Zealand (white) | 1972–1976 | 798 | 2.78 | 6.7 | 5.1 | 5.9 | 1.3 |
| New Zealand | New Zealand (Maori) | 1962–1966 | 25 | 0.19 | 3.0 | 4.6 | 3.6 | 0.7 |
| New Zealand | New Zealand (Maori) | 1972–1976 | 67 | 0.25 | 7.9 | 5.7 | 6.8 | 1.4 |

* Canada is excluded (*see* Table 2)

TABLE 4 AVERAGE ANNUAL AGE-ADJUSTED INCIDENCE RATES/100 000 POPULATION/YR FOR PRIMARY MALIGNANT TUMOURS OF THE NERVOUS SYSTEM FOR 14 EUROPEAN POPULATION GROUPS, 1958–1977

| *Country* | *Region* | *Time period* | *No. of cases* | *Population at risk (in millions)* | *Incidence rates* *Males* | *Females* | *Total* | *Male.Female ratio* |
|---|---|---|---|---|---|---|---|---|
| Denmark | Denmark | 1958–1962 | 1941 | 4.58 | 8.2 | 7.5 | 7.8 | 1.1 |
| Finland | Finland | 1962–1965 | 1071 | 4.56 | 5.9 | 5.7 | 5.8 | 1.0 |
| France | Bas-Rhin | 1975–1977 | 118 | 0.88 | 5.2 | 3.9 | 4.5 | 1.3 |
| France | Doubs | 1977 only | 18 | 0.48 | 3.7 | 3.1 | 3.5 | 1.2 |
| Germany | DDR | 1964–1966 | 2157 | 17.01 | 5.5 | 4.7 | 5.1 | 1.2 |
| Germany | DDR | 1973–1977 | 4876 | 16.86 | 5.8 | 5.1 | 5.4 | 1.1 |
| Germany | FDR | 1963–1966 | 369 | 1.85 | 5.2 | 3.5 | 4.3 | 1.5 |
| Germany | FDR, Hamburg | 1973–1977 | 356 | 1.73 | 4.3 | 2.9 | 3.5 | 1.5 |
| Germany | FDR, Saarland | 1973–1977 | 385 | 1.10 | 7.1 | 5.9 | 6.5 | 1.2 |
| Italy | Verese | 1976–1977 | 92 | 0.78 | 5.8 | 5.3 | 5.6 | 1.1 |
| Norway | Norway | 1964–1966 | 804 | 3.74 | 7.9 | 6.4 | 7.1 | 1.2 |
| Norway | Rural | 1964–1966 | 466 | 2.21 | 7.0 | 5.9 | 6.4 | 1.2 |
| Norway | Urban | 1964–1966 | 428 | 1.53 | 9.3 | 7.0 | 8.1 | 1.3 |
| Switzerland | Geneva | 1973–1977 | 106 | 0.34 | 8.4 | 3.7 | 5.9 | 2.3 |
| Switzerland | Vaud | 1975–1977 | 97 | 0.52 | 6.1 | 4.9 | 5.4 | 1.2 |

TABLE 5 AVERAGE ANNUAL AGE-ADJUSTED INCIDENCE RATES/100 000 POPULATION/YR FOR PRIMARY MALIGNANT TUMOURS OF THE NERVOUS SYSTEM FOR 11 EASTERN AND CENTRAL EUROPEAN POPULATION GROUPS, 1962–1977

| *Country* | *Region* | *Time period* | *No of cases* | *Population at risk (in millions)* | *Incidence rates* *Males* | *Females* | *Total* | *Male Female ratio* |
|---|---|---|---|---|---|---|---|---|
| Hungary | County Miskolc | 1962–1966 | 24 | 0.17 | 2.8 | 2.5 | 2.7 | 1.1 |
| Hungary | County Szabolcs-Szatmar | 1962–1966 | 62 | 0.55 | 3.1 | 1.4 | 2.2 | 2.2 |
| Hungary | County Szabolcs-Szatmar | 1973–1977 | 50 | 0.62 | 1.7 | 1.5 | 1.6 | 1.1 |
| Hungary | County Vas | 1962–1966 | 32 | 0.28 | 1.8 | 2.3 | 2.0 | 0.8 |
| Poland | Cracow city and district | 1965–1966 | 107 | 2.46 | 2.8 | 1.8 | 2.2 | 1.6 |
| Poland | Four rural areas | 1965–1966 | 40 | 0.54 | 4.2 | 3.4 | 3.8 | 1.2 |
| Poland | Katowice district | 1965–1966 | 94 | 3.40 | 1.6 | 1.2 | 1.4 | 1.3 |
| Poland | Warsaw city | 1965–1966 | 196 | 1.25 | 8.4 | 7.6 | 7.8 | 1.1 |
| Poland | Warsaw city | 1973–1977 | 589 | 1.42 | 8.4 | 7.0 | 7.6 | 1.2 |
| Poland | Warsaw rural areas | 1973–1977 | 124 | 0.55 | 6.0 | 3.5 | 4.7 | 1.7 |
| Romania | Banat | 1967 only | 39 | 1.30 | 3.8 | 1.8 | 2.8 | 2.1 |
| Romania | County Cluj | 1974–1978 | 127 | 0.72 | 4.3 | 2.5 | 3.4 | 1.7 |
| Yugoslavia | Slovenia | 1964–1965 | 242 | 1.62 | 3.5 | 2.5 | 2.9 | 1.4 |
| Yugoslavia | Slovenia | 1973–1976 | 230 | 1.78 | 4.1 | 2.6 | 3.3 | 1.6 |

TABLE 6. AVERAGE ANNUAL AGE-ADJUSTED INCIDENCE RATES/100 000 POPULATION/YR FOR PRIMARY MALIGNANT TUMOURS OF THE NERVOUS SYSTEM FOR 14 DIVERSE NON-CAUCASIAN POPULATION GROUPS, 1962-1977

| *Country* | *Region (race)* | *Time period* | *No. of cases* | *Population at risk (in millions)* | *Incidence rates* | | | *Male:Female ratio* |
|---|---|---|---|---|---|---|---|---|
| | | | | | *Males* | *Females* | *Total* | |
| Columbia | Cali | 1962-1966 | 77 | 0.62 | 4.0 | 2.1 | 3.0 | 1.9 |
| Hong Kong | Hong Kong | 1974-1977 | 415 | 4.37 | 2.8 | 2.4 | 2.6 | 1.2 |
| India | Bombay | 1964-1966 | 136 | 4.61 | 1.4 | 1.0 | 1.2 | 1.4 |
| India | Bombay | 1973-1977 | 224 | 6.42 | 1.6 | 1.3 | 1.5 | 1.2 |
| India | Poona | 1973-1977 | 49 | 1.33 | 1.1 | 1.0 | 1.0 | 1.0 |
| Jamaica | Kingston and St Andrews | 1960-1966 | 29 | 0.50 | 2.8 | 1.3 | 2.4 | 2.2 |
| Japan | Miyagi | 1962-1964 | 139 | 1.74 | 3.0 | 2.5 | 2.7 | 1.2 |
| Japan | Miyagi | 1973-1977 | 86 | 1.96 | 1.0 | 0.9 | 0.9 | 1.1 |
| Japan | Nagasaki | 1973-1977 | 51 | 0.45 | 2.9 | 2.3 | 2.5 | 1.3 |
| Japan | Okayama | 1966 | 36 | 1.65 | 2.5 | 1.6 | 2.1 | 1.6 |
| Dutch West Indies | Antilles | 1973-1977 | 21 | 0.18 | 2.3 | 2.4 | 2.4 | 1.0 |
| Nigeria | Ibadan | 1960-1965 | 21 | 0.63 | 1.1 | 0.8 | 1.0 | 1.4 |
| Rhodesia | Bulawayo (African) | 1963-1966 | 13 | 0.17 | 1.9 | 2.0 | 1.9 | 1.0 |
| Senegal | Dakar | 1969-1974 | 52 | 0.70 | 2.0 | 1.4 | 1.7 | 1.4 |
| South Africa | Natal (African) | 1964-1966 | 16 | 0.40 | 1.9 | 1.3 | 1.6 | 1.5 |
| South Africa | Natal (Indian) | 1964-1966 | 11 | 0.27 | 2.7 | 0.3 | 1.7 | 9.0 |

TABLE 7. AVERAGE ANNUAL AGE-ADJUSTED INCIDENCE RATES/100 000 POPULATION/YR FOR PRIMARY MALIGNANT TUMOURS OF THE NERVOUS SYSTEM FOR 5 ISRAELI POPULATION GROUPS OF DIFFERENT ORIGINS, 1960-1966

| *Country* | *Ethnicity* | *Time period* | *No of cases* | *Population at risk (in millions)* | *Incidence rates* | | | *Male:Female ratio* |
|---|---|---|---|---|---|---|---|---|
| | | | | | *Males* | *Females* | *Total* | |
| Israel | All Jews | 1960-1966 | 1466 | 2.12 | 11.4 | 9.8 | 10.7 | 1.2 |
| Israel | Jews born in Europe or America | 1960-1966 | 891 | 0.70 | 14.4 | 13.8 | 14.3 | 1.0 |
| Israel | Jews born in Israel | 1960-1966 | 260 | 0.83 | 8.3 | 10.6 | 9.5 | 0.8 |
| Israel | Jews born in Africa or Asia | 1960-1966 | 315 | 0.58 | 8.4 | 7.8 | 8.1 | 1.1 |
| Israel | Non-Jews (mostly Arabs) | 1960-1966 | 101 | 0.27 | 9.1 | 5.0 | 7.0 | 1.8 |

TABLE 8 AVERAGE ANNUAL AGE-ADJUSTED INCIDENCE RATES/100 000 POPULATION/YR FOR PRIMARY TUMOURS OF THE NERVOUS SYSTEM (REGARDLESS OF THE HISTOLOGIC TYPE) IN 30 DISTINCT POPULATION GROUPS WORLDWIDE, 1968-1977

| *Country* | *Region (ethnicity)* | *Time period* | *No. of cases* | *Population at risk (in millions)* | *Incidence rates* | | | *Male:Female ratio** |
|---|---|---|---|---|---|---|---|---|
| | | | | | *Males* | *Females* | *Total* | |
| Canada | Maritime Provinces | 1973-1977 | 363 | 1.60 | 5.5 | 4.1 | 4.8 | 1.3 |
| China | Shanghai | 1975 | 183 | 5.60 | 3.8 | 3.3 | 3.5 | 1.2 |
| Colombia | Cali | 1972-1977 | 108 | 0.92 | 3.5 | 3.0 | 3.2 | 1.2 |
| Czechoslovakia | Western Slovakia | 1973-1977 | 284 | 1.98 | 3.4 | 2.2 | 2.8 | 1.5 |
| Denmark | Denmark | 1968-1972 | 1692 | 4.92 | 7.2 | 5.3 | 6.2 | 1.4 |
| Denmark | Denmark | 1973-1977 | 1434 | 5.05 | 7.3 | 5.6 | 6.4 | 1.3 |
| Finland | Finland | 1971-1976 | 2053 | 4.67 | 7.2 | 6.1 | 6.6 | 1.2 |
| Israel | Israel (All Jews) | 1972-1976 | 1300 | 2.87 | 9.6 | 8.5 | 9.1 | 1.1 |
| Israel | Israel (Jews born in Africa or Asia) | 1972-1976 | 278 | 0.66 | 8.7 | 6.6 | 7.7 | 1.3 |
| Israel | Israel (Jews born in Europe or America) | 1972-1976 | 626 | 0.80 | 10.8 | 8.9 | 9.8 | 1.2 |
| Israel | Israel (Jews born in Israel) | 1972-1976 | 245 | 1.41 | 9.0 | 8.5 | 8.7 | 1.1 |
| Israel | Israel (Non-Jews) | 1972-1976 | 62 | 0.50 | 3.9 | 2.3 | 3.1 | 1.7 |
| Japan | Osaka | 1973-1977 | 999 | 8.28 | 2.9 | 2.4 | 2.7 | 1.2 |
| Norway | Norway | 1973-1977 | 1747 | 4.00 | 8.6 | 7.3 | 7.9 | 1.2 |
| Poland | Cieszyn | 1973-1977 | 32 | 0.14 | 4.5 | 5.0 | 4.7 | 0.9 |
| Poland | Cracow city and district | 1973-1977 | 264 | 0.68 | 8.1 | 7.8 | 7.8 | 1.0 |
| Poland | Katowice district | 1973-1977 | 239 | 3.72 | 3.9 | 2.8 | 3.3 | 1.4 |
| Poland | Nowy Sacz | 1973-1977 | 70 | 0.20 | 9.2 | 5.2 | 7.1 | 1.8 |
| Singapore | Singapore (Chinese) | 1973-1977 | 125 | 1.68 | 1.6 | 1.7 | 1.7 | 0.9 |
| Singapore | Singapore (Indian) | 1973-1977 | 9 | 0.15 | 1.4 | 0.9 | 1.5 | 1.6 |
| Singapore | Singapore (Malay) | 1973-1977 | 21 | 0.32 | 1.6 | 1.7 | 1.7 | 0.9 |
| Spain | Zaragoza | 1973-1977 | 286 | 0.79 | 6.6 | 5.9 | 6.3 | 1.1 |
| Switzerland | Neuchatel | 1974-1976 | 25 | 0.16 | 5.0 | 4.7 | 4.8 | 1.1 |
| Sweden | Sweden | 1971-1975 | 4943 | 8.14 | 10.0 | 9.9 | 10.0 | 1.0 |
| UK | Birmingham | 1973-1977 | 1424 | 5.18 | 7.3 | 5.6 | 6.4 | 1.3 |
| UK | Thames† | 1973-1977 | 2580 | 6.46 | 7.2 | 6.1 | 6.6 | 1.2 |
| USA | Los Angeles (black) | 1972-1977 | 148 | 0.91 | 4.1 | 2.8 | 3.3 | 1.5 |
| USA | Los Angeles (Chinese) | 1972-1977 | 10 | 0.07 | 3.8 | 2.4 | 3.0 | 1.6 |
| USA | Los Angeles (Japanese) | 1972-1977 | 13 | 0.12 | 2.7 | 1.4 | 2.1 | 1.9 |
| USA | Los Angeles (Spanish) | 1972-1977 | 218 | 1.13 | 4.1 | 3.6 | 3.8 | 1.1 |
| USA | Los Angeles (white) | 1972-1977 | 1641 | 4.94 | 6.1 | 4.4 | 5.2 | 1.4 |

* Average male:female ratio = 1.3 (not weighted for population size).

† Formally South Metropolitan Region.

TABLE 9. COMPARISON OF AVERAGE ANNUAL AGE-ADJUSTED INCIDENCE RATES/100 000/YR FOR PRIMARY TUMOURS OF THE NERVOUS SYSTEM AMONG BLACK, CHINESE, INDIAN AND JAPANESE ETHNIC GROUPS LIVING IN LOCATIONS WIDE APART

| | | | *Incidence rates* | | | |
|---|---|---|---|---|---|---|
| *Ethnic group* | *Location* | *Period* | *Male* | *Female* | *Total* | *Tumour subtype* |
| Black | Jamaica/Kingston and St Andrews | 1960–1966 | 2.8 | 1.3 | 2.4 | Malignant only |
| Black | Senegal/Dakar | 1969–1974 | 2.0 | 1.4 | 1.7 | Malignant only |
| Black | South Africa/Natal | 1964–1966 | 1.9 | 1.3 | 1.6 | Malignant only |
| Black | USA/Atlanta, Georgia | 1975–1977 | 2.7 | 2.4 | 2.6 | Malignant only |
| Black | USA/California, Alameda County | 1973–1977 | 6.2 | 4.4 | 5.3 | Malignant only |
| Black | USA/Detroit, Michigan | 1973–1977 | 4.4 | 2.9 | 3.6 | Malignant only |
| Black | USA/San Francisco Bay | 1973–1977 | 5.7 | 3.9 | 4.7 | Malignant only |
| Chinese | China/Shanghai | 1975 | 3.8 | 3.3 | 3.5 | All tumour types |
| Chinese | USA/Los Angeles | 1972–1977 | 3.8 | 2.4 | 3.0 | All tumour types |
| Chinese | USA/San Francisco Bay | 1973–1977 | 3.1 | 5.8 | 4.4 | Malignant only |
| Chinese | USA/San Francisco Bay | 1973–1977 | 2.5 | 3.9 | 3.2 | Malignant only |
| Indian | India/Bombay | 1964–1966 | 1.4 | 1.0 | 1.2 | Malignant only |
| Indian | India/Bombay | 1973–1975 | 1.6 | 1.2 | 1.5 | Malignant only |
| Indian | South Africa/Natal | 1964–1966 | 2.7 | 0.3 | 1.7 | Malignant only |
| Japanese | Japan/Osaka | 1973–1977 | 2.9 | 2.4 | 2.7 | All tumour types |
| Japanese | USA/Los Angeles | 1973–1977 | 2.7 | 1.4 | 2.1 | All tumour types |
| Japanese | Japan/Miyagi | 1973–1977 | 1.0 | 0.9 | 0.9 | Malignant only |
| Japanese | Japan/Nagasaki | 1973–1977 | 2.9 | 2.3 | 2.5 | Malignant only |
| Japanese | USA/Hawaii | 1973–1977 | 2.1 | 2.2 | 2.1 | Malignant only |
| Japanese | USA/San Francisco | 1973–1977 | 2.3 | 2.3 | 2.2 | Malignant only |

TABLE 10. TEMPORAL TRENDS IN THE AVERAGE ANNUAL AGE-ADJUSTED INCIDENCE RATES/100 000/YR OF PRIMARY MALIGNANT TUMOURS OF THE NERVOUS SYSTEM IN 26 POPULATION GROUPS, EARLY 1960s THROUGH MID-1970s

| *Country* | *Region (race)* | *Time period* | *Total rates* | *Absolute change* |
|---|---|---|---|---|
| Canada | Alberta | 1963–1966 | 4.7 | |
| | | 1970–1972 | 5.5 | +0.8 |
| | | 1973–1977 | 5.4 | −0.1 |
| Canada | British Columbia | 1969–1972 | 6.5 | |
| | | 1973–1977 | 5.6 | −0.9 |
| Canada | Saskatchewan | 1963–1966 | 4.4 | |
| | | 1969–1972 | 5.2 | +0.8 |
| | | 1973–1977 | 5.4 | +0.2 |
| Germany | DDR | 1964–1966 | 5.1 | |
| | | 1968–1972 | 5.4 | +0.3 |
| | | 1973–1977 | 5.4 | None |
| Hungary | County Szabolcs-Szatmar | 1962–1966 | 2.2 | |
| | | 1969–1971 | 1.9 | −0.3 |
| | | 1973–1977 | 1.6 | −0.3 |
| India | Bombay | 1964–1966 | 1.2 | |
| | | 1968–1972 | 1.2 | None |
| | | 1973–1975 | 1.5 | +0.3 |
| Japan | Miyagi | 1962–1964 | 2.7 | |
| | | 1968–1972 | 1.0 | −1.7 |
| | | 1973–1977 | 0.9 | −0.1 |
| Japan | Okayama | 1966 | 2.1 | |
| | | 1969 | 2.4 | +0.3 |
| New Zealand | Maori | 1962–1966 | 3.6 | |
| | | 1968–1971 | 2.7 | −0.9 |
| | | 1972–1976 | 6.8 | +4.1 |
| New Zealand | Non-Maori (mostly Caucasian) | 1962–1966 | 5.9 | |
| | | 1968–1971 | 5.6 | −0.3 |
| | | 1972–1976 | 5.9 | +0.3 |
| Poland | Warsaw City | 1965–1966 | 7.8 | |
| | | 1968–1972 | 7.0 | −0.8 |
| | | 1973–1977 | 7.6 | +0.6 |
| Switzerland | Geneva | 1970–1972 | 5.9 | |
| | | 1973–1977 | 5.9 | None |
| UK | Mersey | 1963–1966 | 6.2 | |
| | | 1968–1972 | 5.9 | −0.3 |
| | | 1975–1977 | 5.2 | −0.7 |
| UK | Oxford | 1963–1966 | 5.1 | |
| | | 1968–1972 | 5.9 | +0.8 |
| | | 1974–1977 | 6.4 | +0.5 |
| UK | Southwestern | 1962–1966 | 6.4 | |
| | | 1966–1970 | 5.6 | −0.8 |
| USA | California, Alameda County (black) | 1960–1964 | 2.1 | |
| | | 1969–1973 | 5.0 | +2.9 |
| | | 1973–1976 | 5.3 | +0.3 |
| USA | California, Alameda County (white) | 1960–1964 | 4.8 | |
| | | 1969–1973 | 6.3 | +1.5 |
| | | 1973–1976 | 6.4 | +0.1 |

TABLE 10 (*cont*)

| *Country* | *Region (race)* | *Time period* | *Total rates* | *Absolute change* |
|---|---|---|---|---|
| USA | Connecticut | 1963–1965 | 5.6 | |
| | | 1968–1972 | 5.4 | −0.2 |
| | | 1973–1976 | 6 2 | +0.8 |
| USA | Hawaii (Caucasian) | 1960–1964 | 4 6 | |
| | | 1968–1972 | 6.6 | +2.0 |
| | | 1973–1977 | 6.3 | −0.3 |
| USA | Hawaii (Chinese) | 1960–1964 | 2.5 | |
| | | 1968–1972 | 2.5 | None |
| | | 1973–1977 | 4.4 | +1.9 |
| USA | Hawaii (Filipino) | 1960–1964 | 3.4 | |
| | | 1968–1972 | 3 3 | −0.1 |
| | | 1973–1977 | 1.7 | −1.6 |
| USA | Hawaii (Hawaiian) | 1960–1964 | 3.0 | |
| | | 1968–1972 | 3.1 | +0.1 |
| | | 1973–1977 | 5 9 | +2.8 |
| USA | Hawaii (Japanese) | 1960–1964 | 2.2 | |
| | | 1968–1972 | 2.6 | +0.4 |
| | | 1973–1977 | 2.1 | −0.5 |
| USA | NY State (excluding NY City) | 1969–1971 | 4.7 | |
| | | 1973–1977 | 5.3 | +0.6 |
| USA | Puerto Rico | 1964–1966 | 1 9 | |
| | | 1968–1972 | 2.3 | +0 4 |
| | | 1973–1977 | 2.3 | None |
| USA | Texas, El Paso (Spanish/Latin) | 1960–1966 | 3.5 | |
| | | 1968–1970 | 4.6 | +1.1 |

TABLE 11. TEMPORAL TRENDS IN THE AVERAGE ANNUAL AGE-ADJUSTED INCIDENCE RATES/100 000/YR FOR ALL PRIMARY TUMOURS OF THE NERVOUS SYSTEM FOR THE LATE 1960s TO THE MID-1970s

| *Country* | *Region (race)* | *Time period* | *Total rates* | *Absolute Change** |
|---|---|---|---|---|
| Colombia | Cali | 1967–1971 | 2.8 | |
| | | 1972–1976 | 3.2 | +0.4 (14.3) |
| Denmark | Denmark | 1963–1967 | 7.9 | |
| | | 1968–1972 | 7.2 | −0.7 (8.9) |
| Denmark | Denmark | 1968–1972 | 6.2 | +0.2 (3.2) |
| | | 1973–1976 | 6.4 | |
| Finland | Finland | 1966–1970 | 6.4 | +0.8 (12.5) |
| | | 1971–1976 | 7.2 | |
| Israel | Israel (All Jews) | 1967–1971 | 11.1 | −2.0 (18) |
| | | 1972–1976 | 9.1 | |
| Israel | Israel (Jews born in Africa or Asia) | 1967–1971 | 7.7 | None |
| | | 1972–1976 | 7.7 | |
| Israel | Israel (Jews born in America or Europe) | 1967–1971 | 10.8 | −1.0 (9.3) |
| | | 1972–1976 | 9.8 | |
| Israel | Israel (Jews born in Israel) | 1967–1971 | 12.3 | −3.6 (29.3) |
| | | 1972–1976 | 8.7 | |
| Israel | Israel (Non-Jews) | 1967–1971 | 4.5 | −1.4 (31.1) |
| | | 1972–1976 | 3.1 | |
| Japan | Osaka | 1970–1971 | 2.6 | |
| | | 1973–1977 | 2.7 | +0.1 (3.8) |
| Norway | Norway | 1968–1971 | 7.1 | |
| | | 1973–1977 | 7.9 | +0.8 (11.3) |
| Poland | Cracow and district | 1968–1972 | 7.1 | |
| | | 1973–1977 | 7.8 | +0.7 (9.9) |
| Poland | Katowice district | 1968–1972 | 3.3 | None |
| | | 1973–1974 | 3.3 | |
| UK | Birmingham | 1968–1972 | 5.4 | |
| | | 1973–1976 | 6.4 | +1.0 (18.5) |
| UK | South Metropolitan | 1967–1971 | 4.8 | |
| | | 1973–1977 | 6.6 | +1.8 (37.5) |

* Figures in parentheses indicate percentage change.

*Brain* (1988), **111**, 757–768

# BOOK REVIEWS

**The Heart and Stroke. Exploring Mutual Cerebrovascular and Cardiovascular Issues.** Edited by Anthony J. Furlan. 1987. Pp. 382. Berlin: Springer. Price £42.00.

This is a worthwhile, imaginative and in places very enjoyable book: worthwhile because it deals with a field athwart the frontiers of neurology and cardiology and thus prone to be misunderstood by practitioners in either specialty, imaginative because it embraces a far wider range of topics than the title suggests, and enjoyable because some of it is very well written.

There are five sections: Cardioembolic Stroke, Cardiovascular Neurobiology, Global Brain Ischaemia, Stoke and Open Heart Surgery, and Epidemiology and Risk Factors. 'Cardioembolic Stroke' starts with a superb essay by C. M. Fisher on the history of cerebral embolism and haemorrhagic infarction. The rest of the section deals at length with causes of stroke, their detection and management. The quality is uneven—there is some repetition and even contradiction between chapters, some amazingly useless statements ('the frequency of systemic embolism in mitral stenosis has been reported to be 10–75%') and some that are just amazing—is isotope ventriculography really better than two dimensional echocardiography in detecting cardiac sources of embolism? The chapter on mitral prolapse and mitral annulus calcification is very well referenced, but which of the studies quoted were good, which bad and which were misleading?

'Cardiovascular Neurobiology' is grandly titled, and deals with the role of the central nervous system in cardiovascular regulation, cardiac dysfunction stroke, and 'Are heart attacks really brain attacks?' (the role of autonomic imbalance in sudden cardiac death). Some good stuff, but heavy going for the mere clinician. After a while one tires of 'so and so says this, somebody that, and someone else disagrees' and longs for the author to say 'but this is how *I* think it works'. Curiously too, hypertension, that great link between stroke and heart disease, makes only a brief appearance here and in the epidemiology section. The 'Global Brain Ischaemia' section is good, with a provocative chapter by Jackson on anoxic encephalopathy following cardiac arrest, a useful survey of orthostatic hypotension, and a sensible, if 'high-tech' discussion of syncope. 'Stroke and Open Heart Surgery' is topical, with a well referenced review of post-bypass neurological deficit and a polarized discussion of carotid endarterectomy from medical and surgical viewpoints. The book ends with the epidemiology section, which includes an admirably clear discussion of risk factor interactions in cardiovascular and cerebrovascular disease based on the Framingham experience.

Dr Furlan is a nice man—some of the contributors actually say so. I think he is too nice—he should buy a big stick and a big blue pencil and lick some of the more recalcitrant contributors into shape. If he can manage this, he has the makings of a classic here.

David de Bono

**Stroke: A Clinical Approach.** By Louis R. Caplan and Robert W. Stein. 1986. Pp. 343. London: Butterworth Price £40.00.

Doctors Caplan and Stein set out to write a book for physicians who care for patients with stroke. Their intended audience includes the general physicians, vascular surgeons and junior hospital doctors who are often involved in the management of patients with stroke whilst lacking specialized training. The evaluation, diagnosis and treatment of the stroke patient are dealt with in pragmatic fashion, frequently by recourse to the single informative case. This is a technique which has become rather unfashionable in medical writing because it unashamedly involves clinical experiences as well as clinical science, and we have all become suspicious of the former. But it is a method which works well in a teaching manual since it mimics the clinical situation. We also gain insight into how two of North America's leading cerebrovascular experts make diagnoses, apply new technologies, and advise on management in patients with the types of acute stroke who, by the apposite choice of case vignette, are all too familiar.

The authors incorporate data from the Harvard and Michael Reese Stroke Registries and, for the most part, are successful in their attempt to apply insights gained from groups to the problems posed by the individual with stroke. In both registries, patients with ischaemic brain infarction are characterized as thrombotic, embolic or lacunar with the implication that each has a distinct pathophysiology which can be recognized clinically with the help of appropriate investigations. But middle cerebral artery thrombosis can present with the clinical and CT appearance of lacunar infarction and patients with internal carotid artery occlusion can suffer delayed ischaemic events from embolic material coursing through the collateral supply. Clinical registries encourage diagnostic consistency by standardizing diagnostic categories but they may preclude fresh insight by imprisoning the clinician within the framework of their preconceptions.

The section on laboratory diagnosis is excellent. The authors elaborate on the established role of CT scanning and angiography, and they offer a brief but critical assessment of noninvasive techniques for assessing the patency and haemodynamic significance of extracranial vascular disease. Xenon rCBF and SPECT get a mention but PET dominates the discussion on functional neuroimaging. The new techniques are critically assessed within the context of patient management and I only have two minor criticisms of this fine chapter. The first concerns the murky quality of the redrawn, rather than photographically reproduced, CT, MRI and PET images. This presumably reflects the decision taken by the publishers to keep costs down. My other worry concerns the pathophysiological role attributed to elevated haematocrit and other factors which affect in vitro blood viscosity. There is mounting evidence to suggest that cerebral blood flow (CBF) varies inversely with haematocrit as a consequence of alterations in arterial oxygen content: factors which influence in vitro blood viscosity do not seem to exert an independent influence on CBF.

Minor criticisms aside, the bulk of the monologue sees Caplan and Stein at their best with eloquent descriptions of the clinical correlates of individual vessel occlusion, cerebral embolism, small vessel disease, hypoxic-ischaemic encephalopathy, intracerebral haemorrhage and subarachnoid haemorrhage. As might be expected, the section on posterior circulation occlusive disease is richly informative. Each chapter is selectively referenced which makes the bibliography particularly useful, in marked contrast with the all too frequent computer search print-outs. Treatment regimes are discussed and the authors unfailingly distinguish between fact and opinion. The final section briefly considers risk factors, complications and rehabilitation, and brief it certainly is with rehabilitation only granted four pages!

In these days of multiple authorship and rather variable editorial control, it is a pleasure to review a book on stroke which has been written by two authors. The style is consistent, repetition is minimal and the book becomes more than the sum of its chapters. I enjoyed their use of the clinical anecdote which seemed appropriate in a book which is essentially a teaching manual. The book admirably fulfils its stated intentions and I would have no hesitation about recommending it for both general and departmental libraries.

JOHN WADE

**Aneurysms Affecting the Nervous System.** By Bryce Weir. 1987. Pp. 671. London: Williams and Wilkins Price £113.00.

Dr Bryce Weir, Professor of Neurosurgery at the University of Alberta, is widely known for his contributions to our understanding of the natural history of ruptured aneurysms and their management. This book marks a further outstanding achievement for which he can be justifiably proud. It is a single-handed review of what is currently known of aneurysms affecting the central nervous system. Dr Weir has thoroughly researched every corner of the literature and seems to have succeeded in including in this book a review of almost everything that is known about aneurysms. Every aspect is thoroughly covered—the history of the subject, the natural history, clinical presentations, investigation, overall management and the details of surgical treatment. References are provided at the end of each section of the book. This book is hardly to be considered as light bedtime reading but it will provide an invaluable and reliable source of information for every neurosurgeon who is concerned with the treatment of aneurysms. It is beautifully produced, well printed and finely illustrated. It is a 'must', not only for every neurosurgical library but for every practising neurosurgeon. Many other fields of neurosurgery would benefit from this sort of exhaustive single author review and one can only hope that Dr Weir's success in this field will be emulated by others.

R. S. MAURICE-WILLIAMS

**Advances in Headache Research.** *Current Problems in Neurology 4.* Edited by F. Clifford Rose. 1987. Pp. 280. London: John Libbey. Price £28.00.

One of the advantages of a special interest in migraine is the abundance of meetings, many in exotic places. Among the longest established of these is the Biennial London Meeting, which has been held since 1966. This book is the selected proceedings of the 6th International Migraine Symposium, held in October 1986. In it a number of leading authorities review many growing points in the painfully slow progress in our understanding of the causes of headache, and of the best way to treat it.

Among the contributors, Solomon and Kappa cogently express our difficulties with diagnostic criteria but then formulate them on a preselected population using the tacit criteria of 'senior neurologists'. Clinical differentiation of all but a minority of headache patients is likely to remain contentious until a biochemical marker is developed. The diagnostic confusion is further enhanced at the end of the book by Mathew's demonstration that the great majority of his large series of patients with chronic daily headache had initially had episodic 'migrainous' pain.

Professor Aristides Leão, from Brazil, who first described spreading depression over 40 years ago, provides an authoritative discussion of its relationship to classical migraine symptoms, and there is further support for this from Schoenen's work on EEG mapping during migraine attacks in the next chapter. Moskowitz, from Boston, has written another outstanding review of his important studies of the nerve supply of cranial vascular structures in the cat, and this is complemented by Lars Edvinsson's analysis of the roles of various neurotransmitters on cortical arterioles.

A number of recent therapeutic developments in migraine are aired. Diclofenac is an effective prophylactic drug and dihydroergotamine seems to be returning to clinical practice, although it has to be administered by nasal spray because of poor absorption by alternative routes. In the study described, formal assessment, unfortunately, was invalidated by the need to practise with the spray for much longer than was anticipated. MacDonald and colleagues describe their problems with the dietary management of children with migraine, Soliman from Paris confirms the lower level of phenol sulphotransferase in diet-sensitive migraine patients first described by Sandler's group, and the latter describe their controlled studies with red wine in such patients, and that extracts of red wine will themselves inhibit the enzyme. Heptinstall attempts a serious analysis of the pharmacological properties of feverfew, and Bousser has shown benefits from percutaneous oestradiol gel in menstrually-linked headaches. A large series of open comparisons from West Germany have suggested that metoprolol, dihydroergotamine, propranolol and flunarizine (in that order) but not nifedipine are effective as migraine prophylactics. Robin Shanks from Belfast provides a masterly analysis of the possible modes of action of betablockers in migraine.

There are seven chapters devoted to cluster headache: for example Lance and Drummond provide evidence that the Horner's syndrome is due to a lesion of the third sympathetic neuron. Rozniecki and colleagues from Poland have shown increased spontaneous basophil degranulation during nitroglycerine-induced attacks, and the Charing Cross group have shown higher leukotriene levels during attacks.

Although much still remains to be elucidated, this book serves to emphasize that there have been a number of exciting developments in recent years, both in pathogenesis and treatment of headache symptoms. Many of the contributors write with considerable authority, though a number of chapters might be regarded only as pilot studies. The book will be invaluable for libraries and for workers in the field—though many of these will have been to the meeting and will have received free or discounted copies. Perhaps it reflects current enthusiasms too much to be recommended as a balanced account for readers without such a special interest.

R. C. PEATFIELD

**Current Therapy in Neurologic Disease—2.** Edited by Richard T. Johnson. 1987. Pp. 367. Oxford: Blackwell, and Philadelphia, PE: B. C. Decker. Price £50.50.

After only two years since the previous edition, with admirable energy the Editor has persuaded 143 contributors—all but 3 are from the North American continent and 2 of the remainder are orthopaedic surgeons writing on peripheral nerve injuries—to compress their opinions on the management of 102 neurological disorders into 356 pages. This formidable task has been achieved by allocating roughly the same space—an average of 2 or 3 pages—for each topic and permitting no allowance for frequency, amenability to specific treatment or controversial therapeutic dilemmas. Apart from a passionate belief in literary democracy and a desire not to alienate one's colleagues, in conceding space to one at the expense of another, it must be presumed that there are other cogent reasons for this drastic policy. For the reviewer the overall effect is odd and is akin to the hope of enlightenment from thumbing through a telephone directory—concise but uninspiring. Thus comparable space is allowed to the management of ubiquitous, taxing and controversial therapeutic challenges such as pain, vertigo and transient ischaemic attacks as to less frequently occurring disorders such as arteriovenous malformations of the brain and spinal cord and Tourette's syndrome. Each contributor has nobly accepted the challenge with considerable ingenuity. For example, where there is no specific treatment, some have expanded into comprehensive lists of differential diagnoses or algorithms concerning decision making—all interesting but not immediately relevant to the avowed intent of the book. Authors of authority have been obliged to cover a controversial topic in a dogmatic, didactic and sketchy manner so that his experience has been encapsulated in very much the same space as a contributor who has little or nothing to say about another topic. Nevertheless, admiration must be confessed for the writer who can wax on the management of the leucodystrophies or sexual problems in spinal cord injury (the latter is the only subject in this compressed volume which has references and suggestions for further reading). It is difficult to imagine the ideal audience for this book, but I doubt whether it will be from readers of this Journal. A previous Editor of *Brain*, who thankfully remains well and busy and might prefer if his name were not mentioned, once reviewed a compendious tome on meningiomas roughly as follows: 'This book is all about removing meningiomas. Those who are in the habit of removing meningiomas will not need this volume; those who do should not be removing meningiomas.' I suspect that his review of the present book might be equally terse.

GERALD STERN

**Epilepsy.** Edited by Anthony Hopkins. 1987. Pp. 585. London: Chapman and Hall. Price £45.00.

This new book on epilepsy is written by 21 authors from the UK and US, with a single author from Poland. The 20 chapters have been tied together by the editor, Anthony Hopkins, who has himself contributed 5 chapters.

The chapter on definition and epidemiology gives a good review of the many epidemiological studies, explaining the reason for different results. That on biology provides a concise, balanced overview of experimental epilepsy and its clinical context. The authors start with the major advances in understanding of the cellular physiology of acute focal epileptic discharges, show how chronic experimental models can help to bridge the gap between these experiments and clinical partial seizures, go on to consider the generalization of partial seizures and the mechanisms of primary generalized seizures, and end with a short review of the many experimental models of epilepsy.

Fritz Dreifuss gives a clear review of the different types of epileptic seizure in terms of the international classification of seizures and syndromes. He stresses the importance of intensive monitoring with video visualization and simultaneous EEG as one of the principal means of achieving accuracy in diagnosis, which is fundamental for the selection of the appropriate therapy. This topic is further elaborated by Colin Binnie in his excellent chapter on EEG, where also 24-hour cassette recording is described with its ability to study the incidence of absence seizures in natural surroundings.

Another interesting chapter by Simon Shorvon on imaging covers all the normally used investigations including CT, MRI and angiography, as well as the more historical air encephalography. PET is also discussed, but not SPECT, although it might be more accessible for most readers.

The important chapter on drug treatment seems to be a little too short, with a rather brief description of the individual antiepileptic drugs. Surprisingly enough, the slow release formulation of carbamazepine does not seem to have been introduced in the UK as yet and is therefore not mentioned. Similarly the two very promising new antiepileptic compounds, which hopefully soon will be on the market—oxcarbazepine and vigabatrin—receive a very superficial description.

There are a number of other good chapters, useful among which is one by Graham Scambler on sociological aspects. It is understood that the current management of epilepsy in the UK, as in many other countries, is largely ritualistic, with unnecessary referral to hospital, unnecessary EEG, inadequate medication, and follow-up supervision not related to patient need. A few commentators—identified as politicians, I suppose—think that epilepsy can generally be managed perfectly adequately in general practice. Epileptologists have lamented the fact that specialized epilepsy centres have not been made available and maintain that this has put people with epilepsy at a disadvantage compared with patients in countries where special epilepsy centres have been established. No doubt clinical aspects of the management of epilepsy can be improved, and it is my feeling that this book may contribute to a better understanding of epilepsy and its correct treatment.

Overall, this is a book I enjoyed reading. I can recommend it to all interested in epilepsy, and perhaps even more to those not interested in epilepsy but who nevertheless take care of patients with this disorder.

MOGENS DAM

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**Advances in Epileptology: XVIth Epilepsy International Symposium.** Edited by P. Wolf, M. Dam, D. Janz and F. Dreifuss. 1987. Pp. 815. New York: Raven Press. Price $199.50.

This volume is based on the proceedings of the XVIth Epilepsy International Congress, held in Hamburg in September 1985, and continues the series of publications from Raven Press of the Epilepsy International Congresses. It is interesting to see how the format of these proceedings has changed over the years. Initially, a slim volume was produced with detailed contributions, and for instance in the edition from the congress 10 years ago, 65 papers only were published. In the new format, contributors have been asked to produce summary papers only (about 4 pages in length), and in this volume there are 169 contributions chosen from the more than 500 presentations at the congress. This is a generally successful policy. The papers are grouped into sections entitled: neuropathology; the electrogenesis of seizures and epilepsy; metabolism; natural history of epilepsy beginning in infancy; semiology; diagnosis, long-term monitoring, and new diagnostic techniques; surgery and epilepsy; role of antiepileptic drugs in the cure of epilepsy; drug therapy and pharmacology; new drugs; pregnancy, offspring and genetics; psychiatric and psychological aspects; development of self-help groups, self-help organizations and their members; biorhythmicity and epilepsy; and a final section entitled Miscellaneous subjects (*sic*). The volume clearly covers a lot of ground, and its main function must be to provide a review of activity in clinical research in epilepsy. Individual contributions are by necessity brief, and much of the better research is published elsewhere in scientific journals in more depth. For an individual wanting a rapid update in any specific research area, or a general review of progress in epilepsy research over the past few years, however, this is a useful volume. The book is well produced and well edited and follows the agreeable style of its predecessors. At a price of $199.50 it is likely to find its way to well endowed libraries only, and to the shelves of only a few individual neurologists.

SIMON SHORVON

**Multiple Sclerosis. Immunological, Diagnostic and Therapeutic Aspects.** Current Problems in Neurology 3. Edited by F. Clifford Rose and Rosemary Jones. 1987. Pp. 260. London: John Libbey. Price £26.00.

Most clinical scientists are familiar with the invitation to speak at a symposium, with subsequent sequential requests for a written abstract followed by demands for a draft for publication. This irritating sequence of events culminates in the production of a book containing data already published, inadequate summaries of work completed and references that are in press. This publication is typical of this process.

A symposium on multiple sclerosis was held at Charing Cross Hospital in late 1986 at which various aspects of the disease were discussed, including those concerned with immunology, diagnosis and therapy. The meeting was valuable for those attending but the publication on this symposium will not be helpful to those clinicians and scientists wishing to glean nuggets of valuable information about the disease. The chapters, all of which are extremely short, vary greatly in content. Some of the immunological work on the pathogenesis of experimental allergic encephalomyelitis reported here is indeed fascinating but mixed up with these chapters are others of no import, such as the bizarre interpretation of epidemiology suggesting a relationship between sinusitis, multiple sclerosis and spirochaetes by Gay and Dick, a view previously aired in that most provocative of journals *The Lancet*. Similarly the section on diagnostic aspects of multiple sclerosis includes articles at the forefront of technological development such as magnetic resonance imaging and central motor conduction time together with commonplace work on evoked potentials and CSF analysis. The weakest section concerns therapy where undue weight is given to diet and oxygen treatment without a word on immunosuppression induced by drugs or radiation.

This is a poor publication that would rightly be unobtainable in 10 years' time if anyone cares to check on a reference to it. It is a pity that a valuable meeting can be spoiled by such an unnecessary publication.

P. RUDGE

**Movement Disorders: a Neuropsychiatric Approach.** By James B. Lohr and Alexander A. Wisniewski. 1987. Pp. 387. Chichester and New York: John Wiley. Price £36.00.

Understanding of movement disorders has, in recent years, undergone a dramatic change with the advent of what may be termed neurochemical neurology, the discovery of L-DOPA, and the implication that many movement disorders seen in clinical practice somehow relate to altered dopamine function within basal ganglia structures. The fact that other areas of the brain often seem to be implicated pathologically in a number of conditions, and that patients with movement disorders display symptoms in addition to pure motor abnormalities often tends to get overlooked, and the neuropsychiatric associations with movement disorders have attracted relatively little interest recently. However, students of movement disorders in the last century were firmly linked to a neuropsychiatric orientation, and a number of obvious facts suggest that a neuropsychiatric approach to movement disorders is as apposite now as it was then. The fact that the word emotion contains within it the word motion suggests that even within our language affective states and movements are closely intertwined, while at the opposite end of the spectrum, at the neurochemical level, transmitters such as dopamine seem related not only to movements, but also to behaviour and its aberrations, notably the major psychoses.

In this book, the authors have adopted a neuropsychiatric approach to an understanding of movement disorders, and it is thus quite different from many contemporary texts on abnormal movements. Even the way the authors have elected to present the conditions under discussion is different, although not original. Thus movements are discussed in two broad categories, namely those of increased and those of decreased movement; within these rubrics conditions such as chorea, athetosis, Parkinson's disease, etc., are considered. However, alongside these are presented such phenomena as complex repetitive movements, states of automatic obedience, cataplexy, startle reactions, catalepsy, negativism and 'complex repetitive movements'. These are followed by sections on disordered muscle tone, and disordered complex motor performance as noted in disorders of expression, posture and gait.

The final section of the book is devoted to special topics which are truly neuropsychiatric, such as the Gilles de la Tourette syndrome and related conditions, catatonia, hysterical conversion disorders, and neuroleptic induced movement disorders.

In the final chapter the authors attempt to synthesize the interface between thought and movement, relating clinical signs and symptoms to the organization of brain function.

For those who wish to be presented with new insights into movement disorders, the book can be recommended, although it is not for the faint-hearted who would surely believe that the sole expression of basal ganglia activity is movement, and that any association with psychiatry is unwarranted and unacceptable. For those who enjoy learning new words, there are many here to practise with, including cheilophagia, contrectation, triakaidekophobia, and kakorraphiophobia.

M. R. Trimble

**Sleep and Its Disorders in Children.** Edited by Christian Guilleminault. 1987. Pp. 334. New York: Raven Press. Price $42.00.

Twenty authors offer 8 chapters about the normal sleep of infants and children and 12 chapters about their abnormal sleep.

A Swedish longitudinal study of a random population of children teaches us that enuresis follows a smooth decline in its prevalence from aged 4 to aged 16 yrs. A third of 18-month-olds engage in rhythmic head-banging and rocking at night and 3% are still doing it at 8 yrs. At least up to 5 yrs, occasional frightened awakenings are so common as to be normal, and under 4% of children are classed as having night terrors, but most of these later become sleepwalkers; 40% of children sleepwalk at some time, the peak age being about 12 yrs. Those who had earlier manifested enuresis have a particular liability to become frequent sleepwalkers. Any link between night terrors and epilepsy is rare, but we read that just sometimes complex partial seizures can present as night terrors.

Obstructive sleep apnoea, even leading to nocturnal anoxic seizures, is discussed in detail. We are reminded of the social disabilities suffered by children with narcolepsy, not least from conflicts with teachers in whose classes they have the impertinence to fall asleep. Two Japanese authors contribute an important chapter on the sleep of mentally retarded and brain-damaged children, in whom it is often difficult to maintain circadian rhythms that follow normal zeitgeibers.

Other authors range over colic, the effects of family stresses such as divorce, and whether children should sleep in their parents' bed (a lot do). Parental mismanagement is easily invoked by smug advisors: fortunately toddlers' sleep disorders improve with time alone. Richard Ferber, from Boston, sensibly remarks that expensive all-night electrophysiological investigations are rarely justified in the face of complaints about a child's sleeplessness. This is a book primarily for the paediatric library.

IAN OSWALD

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**The Lumbar Spine and Back Pain.** Third edition. Edited by Malcolm I. V. Jayson. 1987. Pp. 463. Edinburgh: Churchill Livingstone. Price £60.00.

The reviewer found this book a great disappointment, all the more so because it seemed so attractive at first sight. The superior quality of its printing, paper and illustrations all combined to arouse high expectations which were, sadly, not satisfied by the text.

As with so many current medical books the basic problem appears to be that of multiple authorship. The lumbar spine has become a sort of intellectual no-man's land for the medical profession. A variety of medical and paramedical specialties claim it as their territory and confusion reigns. The connection between symptoms and pathology is frequently obscure and the undoubted role of nonorganic factors in many of its problems is vexed and controversial. No subject is less suitable for the multiauthor approach, for no other subject cries out for the clarity and synthesis which can only be provided by the mind of a single but sceptical authority who has worked out his own approach to its varied problems.

There are a few scattered nuggets of value within this book but much of the text is ill digested and sometimes virtually unreadable. A quarter of the book is occupied by chapters on the biochemistry and biophysics of the spine. These are of little or no relevance to clinical practice and might perhaps have been published in a separate volume.

On the other hand there were some surprising omissions. There is no chapter presenting an overall scheme of practical management of patients synthesized into a single critical viewpoint. Accident neurosis, spinal fusion, spinal tumours and the problem of the failed disc operation receive scant attention. It is curious that three fields which are intimately involved with the practical management of low back problems have provided no contributors—thus the list of authors contains neither a neurosurgeon nor a neurologist, nor does it include a psychiatrist in clinical practice. The omission of a neurosurgeon is striking on two grounds. First, neurosurgeons tend to approach the lumbar spine from a completely different point of view from their orthopaedic colleagues. Secondly, it is largely the neurosurgeon who is left to manage the more complex surgical problems—in particular those generated by unsuccessful previous surgery. It has to be said that many of the opinions and approaches described in this book will seem curious to the neurosurgeon. It is to be feared that this omission may be a reflection of the noncommunication between specialties which so often hinders the treatment of disorders of the lumbar spine Although this book does contain some useful passages and information and some fine illustrations, it cannot on the whole be recommended to the readers of *Brain*.

R. S. MAURICE-WILLIAMS

**Molecular Genetics of Neurological and Neuromuscular Disease.** *Advances in Neurology*, Volume 48. Edited by S. Di Donato, S. DiMauro, A. Memoli and L. P. Rowland. 1988. Pp. 268. New York: Raven Press. Price $62.50.

In recent years no branch of medicine has perhaps benefited more from advances in molecular genetics than neurology. The results of these developments are reflected in novel ways of detecting presymptomatic cases of late onset dominant disorders (such as Huntington's chorea), detecting female carriers of X-linked disorders (such as Duchenne muscular dystrophy), and in prenatal diagnosis. Furthermore, recombinant DNA technology is beginning to reveal details of the molecular pathology of inherited neurological disorders.

Many of these exciting developments are detailed in this edited proceedings of a meeting of experts held in 1986 (not 1983 as given in the Preface!). But because developments in this field are taking place so rapidly, some of the reported findings have already been superseded by more recent work, as in the case of Duchenne muscular dystrophy and the identification of the gene product in this disorder.

The impact of molecular genetics on clinical neurology is well summarized in the introductory chapter by Rowland. The remaining 21 chapters deal mainly with Huntington's chorea, X-linked dystrophy, myotonic dystrophy, various forms of ataxia, peripheral neuropathies and certain mitochondrial disorders. Two subjects perhaps merit special mention. First, 'mitochondrial disorders', where in many cases nuclear gene products are subsequently assembled in the mitochondria, are discussed in relation to cytochrome C oxidase deficiency, various acyl-CoA dehydrogenases, and ornithine transcarbamylase deficiency. Secondly, the identification and characterization of specific mutations in the transthyretin (prealbumin) molecule in various forms of familial amyloid polyneuropathy are detailed. Why mutant forms of transthyretin polymerize into amyloid fibrils, why clinical symptoms do not appear until adult life, and why the peripheral nervous system is predominantly affected in these disorders, are problems which are now beginning to be studied.

There is much to interest and excite neurologists in this latest volume of 'Advances in Neurology', and perhaps in the not too distant future we can hope that molecular studies may also indicate new and rational approaches to treatment for some of these disorders.

ALAN E. H. EMERY

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**Pediatric Neurology and Neuroradiology. Cerebral and Cranial Diseases.** By Claus Dieblen and Olivier Dulac. 1987. Pp. 408. Berlin: Springer. Price DM 298.00.

This well-written book is based on the extensive combined clinical material of a paediatric neurologist and paediatric neuroradiologist. They present in considerable detail and group in logical sequence the clinical, neuropathological and neuroradiological aspects of the disease processes encountered by paediatric neurospecialists. The volume is profusely illustrated with CT sections of excellent quality supplemented by radiographs and angiograms when appropriate. Each illustration is accompanied by an exact description and the caption includes adequate clinical data so that the book can be used equally well as an atlas or as a text and reference book. The material is supplemented by a good background analysis of the relevant literature supported by well selected references and a good index.

Regrettably little magnetic resonance imaging is included; this could limit the appeal of the book in those privileged centres where the modality is fairly freely available. For the present this should not prove a serious drawback outside North America, and the book is highly recommended to those neurologists and radiologists who deal with paediatric patients.

BRIAN KENDALL

**Clinical Applications of Computer Analysis of EEG and Other Neurophysiological Signals.** *Handbook of Electroencephalography and Clinical Neurophysiology*, Volume 2 (Revised Series). Edited by F. H. Lopes da Silva, W. Storm van Leeuwen and A. Rémond. 1986. Pp. 508. Amsterdam: Elsevier. No price stated.

Like all volumes of the *Handbook of Electroencephalography and Clinical Neurophysiology* this book consists of review articles by well-known workers in the field. This new volume is intended to cover 'practical applications' separately from Volume 1, which deals with fundamental aspects. To quote from the introduction: 'This book, we hope, will provide sufficient data for the critical electroencephalographer to weigh the possibilities and the limitations of quantitative clinical neurophysiology made possible by computer applications.'

There are articles on artefacts, monitoring in the laboratory and in the operating theatre (with particular reference to the Prior/Maynard CFM), and the analysis of sleep data, neurometrics, applications in epilepsy, cerebral ischaemia and renal disease, as well as papers on event-related potentials and a discussion of psychoneuropharmacology. There is also a useful set of tables of normative evoked potential data—VEPS to flash and pattern reversal, BAEPs, and SEPs.

The book is largely concerned with computer analysis methods applied to the electroencephalogram but a single chapter by Stålberg and Boon deals with the corresponding position in the allied field of electromyography.

Computing techniques have made much more progress in EMG studies because the function of muscle—to produce force and consequent movement—is much simpler than that of the brain, and physiological models of the functioning of muscle fibres and of peripheral nerve are much better developed, providing a much firmer base for quantitative studies. Concentric needle EMG is the technique which constitutes the foundation of clinical practice and aims to explore the size and spatial extent of motor units and to search for abnormalities of structure, innervation and control of motor unit activity. The human ear is a very sensitive, albeit qualitative, spectrum analyser and very good at detecting changes in the rate of occurrence of discrete sounds. Much of the information gained from electromyographic examination relies on the correlation of these factors with the anatomical position of the needle and the behaviour of the patient. Nevertheless, quantitative techniques which estimate the amount and nature of EMG activity are steadily gaining acceptance. There is also a variety of newer techniques related to the 'single fiber EMG' which are particularly useful for demonstrating abnormalities in neuromuscular transmission and in propagation velocity along muscle fibres. While most of these techniques can be carried out manually they are much more rapidly and reliably carried out by computers.

As far as the analysis of EEG recordings is concerned, although there are very many publications which describe methods of analysing electroencephalograms, there are very few which convincingly report clinical results dependent on such analyses. This volume does something to redress the balance as well as providing comprehensive references to such techniques. Clearly there are formidable problems still to be overcome.

Validation is a very difficult issue and in a contribution on 'Computer analysis of the EEG in epilepsy', Gotman concludes that at least one answer to the disappointing clinical uptake is that the EEGs used in validation studies are all too often not sufficiently similar to those encountered in everyday practice. The most practical systems are those which are employed to scan the very long records obtained in unattended monitoring sessions which store, and subsequently display for the clinical neurophysiologist, brief sections of record containing a suspected epileptiform transient. Attempts to count spikes as an index of epileptiform activity have been widely touted. The spike, although very difficult to characterize precisely, is generally accepted as a reliable 'physical sign' of epilepsy and automatic computerized methods make it possible to obtain reasonably accurate estimates of the rate of spiking activity. The clinical problem, however, is the occurrence of seizures and the predictive ability of spiking for seizure incidence is poor, while other studies suggest that the spiking rate increases *following* a seizure, indicating that the seizure mechanism influences the spike generating mechanism rather than vice versa. Gotman also discusses techniques which attempt to measure the spread of EEG activity in spike-wave episodes and seizures. These techniques have been shown to be useful in defining the focus of origin of epileptic seizures. Anyone familiar with this field will surely agree with the conclusion that 'Although computer technology has evolved even more rapidly than expected, its impact on EEG technology is mainly due to the availability of averagers for evoked potential studies'.

Electromyography is just beginning to feel the impact of computer techniques and this book may have arrived just at the right time to mark the end of an era and the beginning of serious application of computer analysis to electroencephalography as well. It should be read by anyone considering the use of any form of computer in clinical EEG or EMG practice.

H. R. A. TOWNSEND

**The Vertebrate Neuromuscular Junction.** Edited by M. M Salpeter. *Neurology and Neurobiology*, Volume 23. 1987. Pp. 439. New York: Alan Liss. Price £85.00.

The transmission of impulses from nerve to muscle depends on a sequence of events beginning with the opening of presynaptic voltage-dependent $Ca^{++}$ channels in response to an action potential reaching the nerve terminal, followed by $Ca^{++}$-dependent vesicular release of acetylcholine (ACh), binding of ACh to the ACh receptor molecule (AChR), opening of the AChR central pore, influx of $Na^{+}$ ions and the resulting depolarization-dependent activation of the action potential mechanism in the muscle fibre. The whole sequence takes less than 1 ms. The ability to investigate these rapid events in an isolated nerve-muscle preparation has made the neuromuscular junction a prototype for synaptic transmission across all chemical synapses. In addition, the ease with which a nerve or muscle can be manipulated experimentally, and the results studied by a wide variety of morphological, physiological and biochemical techniques, has led to many insights into the development and maintenance of synaptic junctions.

The neuromuscular junction also serves as an example of the way in which knowledge has grown from early studies on physiology and morphology, through pharmacology, biochemistry and electron microscopy, eventually arriving at a molecular view of the processes involved. Several of the chapters in this excellent book illustrate this. In particular M. M. Salpeter, the editor, gives a graphic and beautifully illustrated description of the neuromuscular junction evolving through superb scanning and transmission micrographs to computer simulation of ACh release, diffusion and binding. Thus she establishes in the first chapter a visual picture of the events that will later be analysed in detail.

In a second chapter she describes the changes that occur at the neuromuscular juction during development and after denervation, including a balanced discussion of the relative contribution of trophic factors and activity on maintaining steady-state levels of AChRs. The many studies contributing to our understanding of motoneuron death and the elimination of polyneuronal innervation are discussed by W. J. Betz.

A relatively neglected but increasingly important aspect of the neuromuscular junction is that of the extracellular and subsynaptic matrices. It is now clear that specialized proteins, antigenically different from those found extrajunctionally, guide the formation and maintenance of the neuromuscular junction and are responsible for the accumulation and high density of the proteins involved in transmission—acetylcholine receptors, acetylcholine esterase, etc. The chapter by S. J. Burden summarizes current understanding and is a timely review of a fast-growing field.

Presynaptic functions are detailed by S. W. Jones in a chapter that covers morphology, function of different ion channels, effects of neurotoxins, presynaptic receptors, and cotransmitters, as well as ACh synthesis and packaging. There is a useful analysis of the alternative, nonvesicular, hypothesis of ACh release. Few books on the neuromuscular junction have covered such a wide array of presynaptic functions and approaches to investigation.

Individual chapters are given to the structure, synthesis, turnover and localization of AChE (R. L. Rotundo) and of AChR (D. J. Anderson). Genes for both these proteins have now been cloned and the amino acid sequences derived. Of particular interest are the different molecular forms of AChE, which may partly represent different gene products, and the surprising sequence homology between AChE and thyroglobulin. The section describing approaches to determining the relation between structure and function of the AChR illustrates rather clearly both the usefulness and limitations of sequence data. The following lucid account of the electrophysiology of the AChR (P. R. Adams) also indicates just how much there is still to understand at the molecular level about ACh binding and opening of the ion channel.

Finally, A. G. Engel brings it all into clinical perspective. He discusses the safety factor in transmission, experimentally induced defects in neuromuscular transmission, and the relevant human disorders. It is particularly gratifying to see how clinical science has been able to utilize scientific developments to understand disease. Whereas 30 years ago any defect in neuromuscular transmission was likely to be labelled as myasthenia gravis it is now clear that there are autoimmune and congenital conditions, both presynaptic and postsynaptic. Each can be shown to involve a particular function, and in the case of autoimmune conditions (the Lambert-Eaton syndrome which affects the presynaptic voltage-dependent $Ca^{++}$ channels, and myasthenia gravis that affects acetylcholine receptors) IgG has been demonstrated at the relevant site by Engel and his colleagues.

This is a beautifully written, detailed, and very well referenced book which will be a delight to own. Many of the chapters cover areas which are fairly familiar, but others discuss newer work which it is difficult to find summarized so lucidly elsewhere. It will be of great use to serious researchers of the neuromuscular junction, at whatever level, but might be a little overwhelming for anyone who is not yet committed to this field. Nevertheless the high standard and clarity of the writing and the excellent illustrations in each chapter make it a marvellous book to dip into, and should attract the more casual reader from other disciplines who will see how scientific progress has evolved to the point of explaining disease processes.

Angela Vincent

## ANNOUNCEMENTS

### American Association for Electromyography and Electrodiagnosis

The 35th Annual Meeting of the AAEE will be held in San Diego, California, on October 7-8, 1988. Further information may be obtained from Ella Van Laningham, AAEE Executive Director, 732 Marquette Bank Building, Rochester, MN 55904 (Tel. 507-288 0100). It will be preceded by a joint symposium with the American Electroencephalographic Society on Somatosensory Evoked Potentials and Electric and Magnetic Coil Stimulation on October 5 and the AAEE 11th Annual Continuing Education Courses and Workshops on October 6.

### Biological Engineering Society

A meeting on Electrical Stimulation of Muscle will be held on January 19-20, 1989, at Hexham General Hospital, Northumberland. Abstracts (200 words) should be sent to Mr G. Creasey, Spinal Unit, Edenhall Hospital, Musselburgh, Edinburgh EH21 772 by September 1, 1988. Details of the meeting may be obtained from Dr R J Minns, Regional Medical Physics Department, Durham Unit, Dryburn Hospital, Durham (Tel. 091-386 4911)

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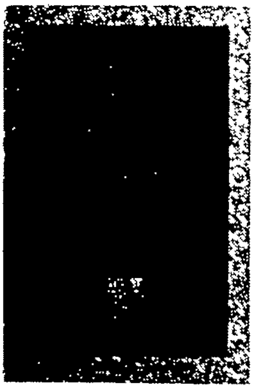

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1. The primary purpose of such grants is to facilitate short visits to laboratories or departments of particular relevance to the applicant's research. Applications cannot be entertained without the following documents:
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Four copies of all documents should be submitted to

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